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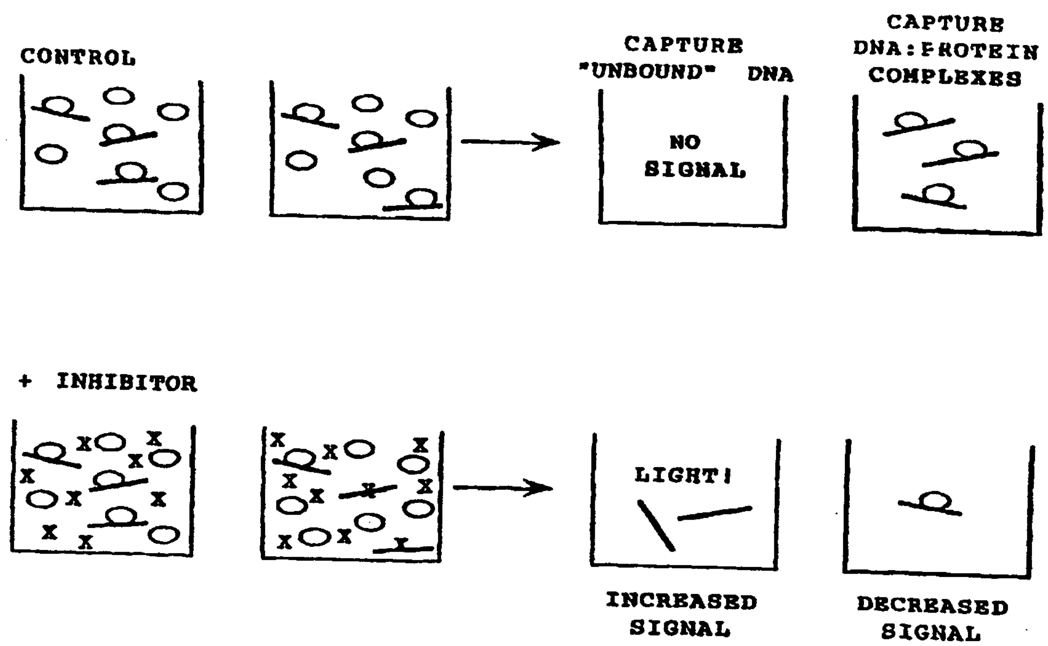

(57) Abstract

The present invention defines a DNA protein-binding assay useful for screening libraries of synthetic or biological compounds for their ability to bind DNA test sequences. The assay is versatile in that any number of test sequences can be tested by placing the test sequence adjacent to a defined protein-binding screening sequence. Binding of molecules to these test sequence changes the binding characteristics of the protein molecule to its cognate binding sequence. When such a molecule binds the test sequence the equilibrium of the DNA:protein complexes is disturbed, generating changes in the concentration of free DNA probe. Numerous exemplary target test sequences (SEQ ID NO:1 to SEQ ID NO:600) are set forth. The assay of the present invention is also useful to characterize the preferred binding sequences of any selected DNA-binding molecule.

SEQUENCE-DIRECTED DNA-BINDING MOLECULES COMPOSITIONS AND METHODS

Field of the Invention

The present invention relates to methods, systems, and kits useful for the identification of molecules that specifically bind to defined nucleic acid sequences. Also described are methods for designing molecules having the ability to bind defined nucleic acid sequences and compositions thereof.

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References

Ambinder, R.F., *et al.*, *J. Virol.* 65:1466-1478 (1991).

Angel, P., et al., Nature 332:166 (1988).

Ausubel, F. M., *et al.*, Current Protocols in Molecular Biology, John Wiley and Sons, Inc., Media PA.

Baguley, B.C., *Mol. Cell. Bioch.* 43:167-181 (1982).

Banerji, S.S., *et al.*, *Mol. Cell Biol.* 11:4074-4087 (1991).

Beal, P.A., *et al.*, *Science* 251:1360-1363 (1991).

Becker, Y., *et al.*, *Isr. J. Med. Sci.* 8:1225 (1972).

Bialer, M., *et al.*, *J. Med. Chem.* 23:1144 (1980).

Bialer, M., *et al.*, *J. Pharm. Sci.* 70:822 (1981).

Birg, F., *et al.*, *Nucl. Acids Res.* 18:2901-2908 (1990).

Bohmann, D., et al., Science 238:1386 (1987).

Bos, T.J., et al., Cell 52:705 (1988).

Chaiet, L., et al., *Arch. Biochem. Biophys.* 106:1 (1964).

Chaires, J.B., et al., *Biochemistry* 29:6145-6153 (1990).

Chang, H.-K,, *et al.*, *Mol. Cell. Biol. November*:-5189-5197 (1989).

Chen, K-X., *et al.*, *J. Biomol. Struct. Dyn.* 3:445-466 (1985).

Chin, M.T., *et al.*, *J. Virol.* 63:2967-2976 (1989).

Comai, L., *et al.*, *Cell* 68:965-976 (1992).

Cooney, M., *et al.*, *Science* 241:456-459 (1988).

Courtois, G., *et al.*, *Proc. Natl. Acad. Sci. USA* 85:7937-7941 (1988).

Cullinane, C., *et al.*, *FEBS Lett.* 293:195-198 (1991).

Debart, F., *et al.*, *J. Med. Chem.* 32:1074 (1989).

Dervan, P.B., *Science* 232:464-471 (1986).

Descheemaeker, K.A., *et al.*, *J. Biol. Chem.* 267(21):15086 (1992).

Edwards, C.A. *et al.*, *J. Mol. Biol.* 180:73-90 (1984).

Edwards, C.A., *et al.*, in: Advances in Regulation of Cell Growth, Volume I: Regulation of Cell Growth and Activation, edited by Mond, J.J., *et al.*, New York: Raven Press, p. 91-118 (1989).

Elias, P., *et al.*, *Proc. Natl. Acad. Sci.* USA 85:2959-2963 (1988).

Fox, K.R., *et al.*, *Biochim. Biophys. Acta* 840:383-392 (1985).

Fox, K.R., *et al.*, *Nucl. Acids Res.* 16:2489-2507 (1988).

Fox, K.R., *et al.*, *Nucl. Acids Res.* 18:1957-1963 (1990).

Fox, K.R., *et al.*, *Biochem J.* 269:217-221.

Fried, M.G., *et al.*, *Nuc. Acid. Res.* 9:6505 (1981).

Galas, D., *et al.*, *Nuc. Acid Res.* 5:3157-3170 (1981).

Garner, M.M., *et al.*, *Nuc. Acid. Res.* 9:3047 (1981).

Gaugain, B., *et al.*, *Biochemistry* 17:5071 (1978).

Gessner, R.V., *et al.*, *Biochemistry* 24:237-240 (1985).

Gilbert, D.F., *et al.*, *Proc. Natl. Acad. Sci. USA* 86:3006 (1988)

Gilman, A. G., *et al.*, eds., The Pharmacological Basis of Therapeutics, Eighth Edition, Pergamon Press (1990).

Goldin, A.L., *et al.*, *J. Virol.* 38:5-58 (1981).

Goodisman, J., *et al.*, *Biochemistry* 31:1046-1058 (1992).

Green, N.M., *Adv. Protein Chem.* 29:85 (1975).

Greenblatt, J., *Cell* 66:1067-1070 (1991).

Greene, W.C., *Annu. Rev. Immunol.* 8:453-475 (1990).

Griffen, J.H., *et al.*, *J. Am. CHem. Soc.* (1992).

Griffin, L.C., *et al.*, *Science* 245:967-971 (1989).

Gross, D.S., *et al.*, *Annu.Rev.Biochem.* 57:159-197 (1988).

Gurskii, G.V., *et al.*, *Mol. Biol.* 19:177 (1985).

Harlow, E., *et al.*, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press (1988).

Harshman, K.D., et al., Cell 53:321 (1988).

Hausheer, F.H., *et al.*, *Anti-Cancer Drug Design* 5:159-167 (1990).

Hawley, R.C., *et al.*, *Proc. Natl. Acad. Sci. USA* 86:1105-1109 (1989).

Helene, C., *et al.*, *Biochim. Biophys. Acta* 1049:99-125 (1990).

Helene, C., et al., *Genome* 31:413-420 (1989).

Hoogsteen, *Acta Cryst.* 12 822 (1959).

Innis et al., eds. PCR Protocols, a Guide to Methods and Applications, Academic Press, Inc. (1991).

Jain, S.C., et al., *J. Mol. Biol.* 68:1-20 (1972).

Jeppesen, C., et al., *Eur. J. Biochem.* 182:437-444 (1989).

Kadonaga, J.T., *PNAS* 83:5889-5893 (1986).

Kissinger, K., et al., *Biochemistry* 26:5590 (1987).

Kitadai, Y., et al., *Biochem. Biophys. Res. Commun.* 189(3):1342 (1992).

Koff, A., et al., *J. Virol.* 62:4096-4103 (1988).

Kotler, M., et al., *FEBS.Lett.* 21:222 (1972).

Krowicki, K., et al., *J. Org. Chem.* 52:3493 (1987).

Kuhlmann, K.F., et al., *Nucl. Acids Res.* 5:2629 (1978).

Laugaa, P., et al., *Biochemistry* 23:1336 (1985).

Le Pecq, J.B., et al., *Proc. Natl. Acad. Sci. U.S.A.* 72:2915-2919 (1975).

Lee, D.K., et al., *Cell* 67:1241-1250 (1991).

Lown, J.W., et al., *J. Org. Chem.* 50:3774 (1985).

Lown, J.W., et al., *J. Med. Chem.* 29:1210 (1986).

Luck, G., et al., *Nucl. Acids Res.* 1:503 (1974).

Luckow, V.A., et al., *Virology* 170:31 (1989).

Maher III, L.J., et al., *Science* 245:725-730 (1989).

Maher, L.J., et al., *Biochemistry* 31(1):70-81 (1992).

Maniatis, T., et al. Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory (1982).

Maxam, A.M., et al., *Meth. Enzymol.*, 65:499 (1980).

McGeoch, D.J., *et al.*, *J. Virol.* 62:444-453 (1988).

Meijer, I., *et al.*, *Cell-Immunol.* 145(1):56 (1992).

Miller, *et al.*, U.S. Patent No. 4,757,055, issued 19 July 1988.

Montenay-Garestier, T., *et al.*, *CIBA Found. Symp.* 158:147-157.

Mullis, K.B., U.S. Patent No. 4,683,202, issued 28 July 1987.

Mullis, K.B., *et al.*, U.S. Patent No. 4,683,195, issued 28 July 1987.

Nakamura, S., *et al.*, *J. Antiobiot., Ser. A.* 17:220 (1964).

Neuberg, M., *et al.*, *Oncogene* 6(8):1325 (1991).

Olivo, P.D., *et al.*, *Proc. Natl. Acad. Sci. USA* 85:5414-5418 (1988).

Olivo, P.D., *et al.*, *J. Virology* 3:196-204 (1989).

Pelaprat, D., *et al.*, *J. Med. Chem.* 23:1336-1343 (1980).

Perouault, L., *et al.*, *Nature* 344:358-360 (1990).

Phillips, D.R., Anti Cancer Drug Design 5:21-29 (1990).

Phillips, et *al.*, Biochemisty 29:4812-4819 (1990).

Pitha, *Biochem. Biophys. Acta* 204:39 (1970a).

Pitha, *Biopolymers* 9:965 (1970b).

Portugal, J., *et al.*, *FEBS Lett.* 225:195-200 (1987).

Quigley, G.J., *et al.*, *Science* 232:1255-1258 (1986).

Raney, A.K., *et al.*, *J. Virol.* 66(12):6912 (1992).

Reisman, D., *et al.*, *Mol. Cell. Biol.* 5:1822-1832 (1985).

Remers, W.A., Antineoplastic Agents, New York: John Wiley and Sons, Inc., 1992.

Rice, J.A., *et al.*, *Proc. Natl. Acad. Sci. USA* 85:4158-4161 (1988).

Ryder, K., et al., Proc. Natl. Acad. Sci. USA 85:1487 (1988).

Salas, X., *et al.*, *FEBS Lett.* 292:223-228 (1991).

Sambrook, J., *et al.*, In Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Vol. 2 (1989).

Sanger, F., et al., Proc Nat Acad Sci, USA, 74:5363 (1977).

Schmidt, A., *et al.*, *J. Virol.* 64:4037-4041 (1990).

Schultz, P.G., *et al.*, *Proc. Natl. Acad. Sci. USA* 80:6834-6837 (1983).

Schuhmann, E., *et al.*, *Allg. Microbiol.* 14:321 (1974).

Shaw, J.P., et al., Science 241:202 (1988).

Sherman, S.E., *et al.*, *Chem. Rev.* 87:1153 (1987).

Siebenlist, U., *et al.*, *Proc. Natl. Acad. Sci. USA* 77:122-126 (1980).

Skorobogaty, A., *et al.*, *Anti-Cancer Drug Design* 3:41-56 (1988).

Smith, D.B., *et al.*, *Gene* 67:31 (1988).

Sobell, H.M., *et al.*, *J. Mol. Biol.* 68:21-34 (1972).

Sobell, H.M., *Prof. Nucl. Acid. Res. Mol. Biol.* 13:153-190 (1973).

Stow, N.D., *et al.*, *Virology* 130:427-438 (1983).

Stow, N.D., *et al.*, *J. Gen. Virol.* 67:1613-1623 (1986).

Strobel, S.A., *et al.*, *Science* 249:73-75 (1990).

Summers, M.D., *et al.*, A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures, Texas Agricultural Experimental Station Bulletin, No. 1555 (1987).

Summerton, J., *et al.*, PCT International Application, Publication No. WO 86/05518, Published 25 September 1986.

Summerton, J., *et al.*, U.S. Patent No. 5,034,506, issued 23 July 1991.

Thompson, C.B., *et al.*, *Molecular and Cell Biology* 12(3):1043 (1992).

Thrum, H., *et al.*, Antiomicrobial and Antineoplastic Chemotherapy, Prague: Czech. Med. Press, pp. 819-822 (1972).

Tullius, T.D., *Ann. Rev. Biophys. Biochem.* 18:213-237 (1989).

Wang, A.H.-J., *et al.*, *Science* 225:1115-1121 (1984).

Wartel, R.M., *et al.*, *J. Biol. Chem.* 15:285-318 (1975).

Weir, H.M., *et al.*, *Nucl. Acids Res.* 17:1409-1425 (1989).

Werner, G.H., *et al.*, *Actual. Pharmaceut. Fr.* 21:133 (1963).

White, R.J., *et al.*, *Biochemistry* 28:6259-6269 (1989).

Wirth, T., *et al.*, *EMBO J.* 7(10):3109 (1988).

Woodbury, C.P., *et al.*, *Biochemistry* 22(20):4730-4737 (1983).

Wu, C.A., *et al.*, *J. Virol.* 62:435-443 (1988).

Young, S.L., *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 88:10023-10026 (1991).

Zein, N., *et al.*, *Science* 240:1198 (1988).

Zimmer, C., *Pros. Nucl. Acid Res. Mol. Biol.* 15:285-318 (1975).

Background of the Invention

Several classes of small molecules that interact with double-stranded DNA have been identified. Many of

these small molecules have profound biological effects. For example, many aminoacridines and polycyclic hydrocarbons bind DNA and are mutagenic, teratogenic, or carcinogenic. Other small molecules that bind DNA include: biological metabolites, some of which have applications as antibiotics and antitumor agents including actinomycin D, echinomycin, distamycin, and calicheamicin; planar dyes, such as ethidium and acridine orange; and molecules that contain heavy metals, such as cisplatin, a potent antitumor drug.

The sequence binding preferences of most known DNA binding molecules have not, to date, been identified. However, several small DNA-binding molecules have been shown to preferentially recognize specific nucleotide sequences, for example: echinomycin has been shown to preferentially bind the sequence [(A/T)CGT]/[ACG(A/T)] (Gilbert *et al.*); cisplatin has been shown to covalently cross-link a platinum molecule between the N7 atoms of two adjacent deoxyguanosines (Sherman *et al.*); and calicheamicin has been shown to preferentially bind and cleave the sequence TCCT/AGGA (Zein *et al.*).

Many therapeutic DNA-binding molecules (such as distamycin) that were initially identified based on their therapeutic activity in a biological screen have been later determined to bind DNA. There are several examples in the literature referring to synthetic or naturally-occurring polymers of DNA-binding drugs. Netropsin, for example, is a naturally-occurring oligopeptide that binds to the minor groove of double-stranded DNA. Netropsin contains two 4-amino-1-methylpyrrole-2-carboxylate residues and belongs to a family of similar biological metabolites from *Streptomyces spp.* This family includes distamycin, anthelvencin (both of which contain three N-methylpyrrole residues), noformycin, amidomycin (both of which

contain one N-methylpyrrole residue) and kikumycin (which contains two N-methylpyrrole residues, like netropsin) (Debart, *et al.*). Synthetic molecules of this family have also been described, including the above-mentioned molecules (Lown, *et al.* 1985) well as dimeric derivatives (Griffin *et al.*, Gurskii, *et al.*) and certain analogues (Bialer, *et al.* 1980, Bialer, *et al.* 1981, Krowicki, *et al.*).

Molecules in this family, particularly netropsin and distamycin, have been of interest because of their biological activity as antibacterial (Thrum *et al.*, Schuhmann, *et al.*), antiparasitic (Nakamura *et al.*), and antiviral drugs (Becker, *et al.*, Lown, *et al.* 1986, Werner, *et al.*).

Among the synthetic analogs of netropsin and distamycin are oligopeptides that have been designed to have sequence preferences different from their parent molecules. Such oligopeptides include the "lexitropsin" series of analogues. The N-methlypyrrole groups of the netropsin series were systematically replaced with N-methylimidazole residues, resulting in lexitropsins with increased and altered sequence specificities from the parent compounds (Kissinger, *et al.*). Further, a number of poly(N-methylpyrrolyl)-netropsin analogues have been designed and synthesized which extend the number of residues in the oligopeptides to increase the size of the binding site (Dervan, 1986).

There are several different approaches that could be taken to look for small molecules that specifically inhibit the interaction of a given DNA-binding protein with its binding sequence (cognate site). One approach would be to test biological or chemical compounds for their ability to preferentially block the binding of one specific DNA:protein interaction but not others.

Such an assay would depend on the development of at least two, preferably three, DNA:protein interaction systems in order to establish controls for distinguishing between general DNA-binding molecules (polycations like heparin or intercalating agents like ethidium) and DNA-binding molecules having sequence binding preferences that would affect protein/cognate binding site interactions in one system but not the other(s).

One illustration of how this system could be used is as follows. Each cognate site could be placed 5' to a reporter gene (such as genes encoding β-galactoside or luciferase) such that binding of the protein to the cognate site would enhance transcription of the reporter gene. The presence of a sequence-specific DNA-binding drug that blocked the DNA:protein interaction would decrease the enhancement of the reporter gene expression. Several DNA enhancers could be coupled to reporter genes, then each construct compared to one another in the presence or absence of small DNA-binding test molecules. In the case where multiple protein/cognate binding sites are used for screening, a competitive inhibitor that blocks one interaction but not the others could be identified by the lack of transcription of a reporter gene in a transfected cell line or in an *in vitro* assay. Only one such DNA-binding sequence, specific for the protein of interest, could be screened with each assay system. This approach has a number of limitations including limited testing capability and the need to construct the appropriate reporter system for each different protein/cognate site of interest.

Another example of a system to detect sequence-specific DNA-binding molecules would involve cloning a DNA-binding protein of interest, expressing the protein in an expression system (*e.g.*, bacterial, baculovirus,

or mammalian expression systems), preparing a purified or partially purified sample of protein, then using the protein in an *in vitro* competition assay to detect molecules that blocked the DNA:protein interaction. These types of systems are analogous to many receptor:ligand or enzyme:substrate screening assays developed in the past, but have the same limitations as outlined above in that a new system must be developed for every different protein/cognate site combination of interest. The capacity for screening numerous different sequences is therefore limited.

Another example of a system designed to detect sequence-specific DNA-binding drugs would be the use of DNA footprinting procedures as described in the literature. These methods include DNase I or other nuclease footprinting (Chaires, *et al.*), hydroxy radical footprinting (Portugal, *et al.*), methidiumpropyl EDTA(iron) complex footprinting (Schultz, *et al.*), photofootprinting (Jeppesen, *et al.*), and bidirectional transcription footprinting (White, *et al.*). These procedures are likely to be accurate within the limits of their sequence testing capability but are seriously limited by (i) the number of different DNA sequences that can be used in one experiment (typically one test sequence that represents the binding site of the DNA-binding protein under study), and (ii) the difficulty of developing high throughput screening systems.

Summary of the Invention

In one aspect, the invention includes a method of constructing a DNA-binding agent capable of sequence-specific binding to a duplex DNA target region. The method includes identifying in the duplex DNA, a target region containing a series of at least two non-overlapping base-pair sequences of four base-pairs each, where

the four base-pair sequences are adjacent, and each sequence is characterized by sequence-preferential binding to a duplex DNA-binding small molecule. The small molecules are coupled to form a DNA-binding agent capable of sequence-specific binding to said target region.

In one embodiment, the duplex-binding small molecules are identified as molecules capable of binding to a selected test sequence in a duplex DNA by first adding a molecule to be screened to a test system composed of (a) a DNA-binding protein that is effective to bind to a screening sequence in a duplex DNA, with a binding affinity that is substantially independent of the test sequence adjacent the screening sequence, but that is sensitive to binding of molecules to such test sequence, when the test sequence is adjacent the screening sequence, and (b) a duplex DNA having said screening and test sequences adjacent one another, where the binding protein is present in an amount that saturates the screening sequence in the duplex DNA.

The test molecule is incubated in the test system for a period sufficient to permit binding of the molecule being tested to the test sequence in the duplex DNA. The degree of binding protein bound to the duplex DNA before adding the test molecule is compared with that after adding the molecule. The screening sequence may be from the HSV origin of replication, and the binding protein may be UL9. Exemplary screening sequences are identified as SEQ ID NO:601, SEQ ID NO:602, SEQ ID NO:615, and SEQ ID NO:641.

Specific examples of tetrameric basepair sequences include TTTC, TTTG, TTAC, TTAG, TTGC, TTGG, TTCC, TTCG, TATC, TATG, TAAC, TAAG, TAGC, TAGG, TACC, TAGC sequences. A specific example of a small molecule capable of binding to these sequences is distamycin.

In another aspect, the invention includes a method of blocking transcriptional activity from a duplex DNA template. The method includes identifying in the duplex DNA, a binding site for a transcription factor and, adjacent the binding site, a target region having a series of at least two non-overlapping tetrameric base-pair sequences, where the four (tetrameric) base-pair sequences are adjacent and each sequence is characterized by sequence-preferential binding to a duplex DNA-binding small molecule. The sequences are contacted with a binding agent composed of the small molecules coupled to form a DNA-binding agent capable of sequence-specific binding to said target region.

The target may be selected, for example, from DNA sequences adjacent a binding site for a eucaryotic transcription factor, such as transcription factor TFIID, or a procaryotic transcription factor, such as transcription sigma factor.

For mammalian transcription factors, the target region is typically chosen from non-conserved regions adjacent the transcription factor binding site. Target regions can be chosen so that the small molecule binding overlaps an adjacent transcription factor DNA binding sequence (*e.g.*, for a TFIID binding site, by 1-3 nucleotide pairs). In this case, the specificity of DNA binding for the small molecule is essentially derived from the non-conserved sequences adjacent the transcription factor binding site, in order to reduce small molecule binding at the transcription factor binding site associated with other genes.

Also disclosed is a DNA-binding agent capable of binding with base-sequence specificity to a target region in duplex DNA, where the target region contains at least two adjacent four base-pair sequences. The agent includes at least two subunits, where each

subunit is a small molecule which has a sequence-preferential binding affinity for a sequence of four base-pairs in the target region. The subunits are coupled to form a DNA-binding agent capable of sequence-specific binding to said target region.

In one general embodiment, the agent is designed for binding to a sequence in which the two tetrameric basepair sequences are separated (for example, by up to 20 basepairs, typically, 1 to 6 basepairs) and the small molecules in the agent are coupled to each other by a spacer molecule.

Also forming part of the invention is a method of constructing a binding agent capable of sequence-specific binding to a duplex DNA target region. The method includes identifying in the duplex DNA, a target region containing (i) a series of at least two adjacent non-overlapping base-pair sequences of four base-pairs each, where each four base-pair sequence is characterized by sequence-preferential biding to a duplex DNA-binding small molecule, and (ii) adjacent to (i) a DNA duplex region capable of forming a triplex with a third-strand oligonucleotide. The two small molecules are coupled to form a DNA-binding agent capable of sequence-specific binding to said target region, and the DNA-binding agent is attached to a third-strand oligonucleotide.

The binding of the DNA-binding agent to duplex DNA causes a shift from B form to A form DNA, allowing triplex binding between the third-strand polynucleotide and a portion of the target sequence.

Also disclosed is a triple-strand forming agent for use in practicing the method.

In still another aspect, the invention includes a method of ordering the sequence binding preferences a DNA-binding molecule. The method includes adding a

molecule to be screened to a test system composed of (a) a DNA-binding protein that is effective to bind to a screening sequence in a duplex DNA with a binding affinity that is substantially independent of such test sequence adjacent the screening sequence, but that is sensitive to binding of molecules to such test sequence, and (b) a duplex DNA having said screening and test sequences adjacent one another, where the binding protein is present in an amount that saturates the screening sequence in the duplex DNA. The molecule in the test system is incubated for a period sufficient to permit binding of the molecule being tested to the test sequence in the duplex DNA, and the amount of binding protein bound to the duplex DNA before and after addition of the test molecule is compared. These steps are repeated using all test sequences of interest, and the sequences are then ordered on the basis of relative amounts of protein bound in the presence of the molecule for each test sequence.

The test sequences are selected, for example, from the group of 256 possible four base sequences composed of A, G, C and T. The DNA screening sequence is preferably from the HSV origin of replication, and the binding protein is preferably UL9.

The invention also includes, a method for altering the binding characteristics of a DNA-binding protein to a duplex DNA. In the method, a binding site for the DNA-binding protein is identified in the duplex DNA and a target region identified adjacent the binding site. A small molecule is selected that is characterized by sequence-preferential binding to the target region. Such molecules can be selected by the assay and methods of the present invention. When the small molecule is bound to the target region, the small molecule is typically adjacent to the binding site for the DNA-

binding protein. Alternatively, the binding of the small molecule may overlapping the site for the DNA-binding protein by at least one nucleotide pair. In the case of such overlap, the specificity of DNA binding for the small molecule is essentially derived from non-conserved sequences adjacent the DNA-binding protein's binding site -- in order to reduce small molecule binding at similar DNA:protein binding sites at other locations. Finally,
the duplex DNA is contacted with the small molecule at a concentration effective to alter binding of the DNA-binding protein to its binding site.

In this method, contacting the duplex DNA with a small molecule can either inhibit or enhance the binding of the DNA-binding protein to its binding site: depending on the small molecule that is selected. Exemplary DNA binding proteins include DNA replication factors and a variety of transcription factors.

One application of this method is to eucaryotic general transcription factors (*e.g.*, TFIID), where the target region is typically selected from DNA sequences adjacent the binding site for the eucaryotic transcription factor (*e.g.*, SEQ ID NO:1 to SEQ ID NO:600). In one embodiment, the DNA binding protein is a eucaryotic general transcription factor and the small molecule binds, in addition to the target region, 1 to three nucleotide pairs of the DNA-binding protein's binding site. In the case of TFIID, the small molecule typically binds to (i) the target region, and (ii) up to two nucleotides of the binding site for TFIID, where the nucleotides are contiguous to the target region.

Generally, the present invention provides a method of screening for molecules capable of binding to a selected test sequence in a duplex DNA. In the method of the present invention a test sequence of interest is

selected. Such sequences can be selected, for example, from the group of sequences presented as SEQ ID NO:1 to SEQ ID NO:600. Alternatively, the test sequences can be sequences having randomly generated sequences or defined sets of sequences, such as, the group of 256 possible four base sequences composed of A, G, C and T.

A duplex DNA test oligonucleotide is constructed having a screening sequence adjacent a selected test sequence, where a DNA binding protein is effective to bind to the screening sequence with a binding affinity that is substantially independent of the adjacent test sequence. In such constructs the DNA protein binding to the screening sequence is sensitive to binding of test molecules to the test sequence.

Molecules selected for testing/screening are added to a test system composed of (a) the DNA binding protein, and (b) the duplex DNA test oligonucleotide, which contains the screening and test sequences adjacent one another. Selected molecules are incubated in the test system for a period sufficient to permit binding of the molecule being tested to the test sequence in the duplex DNA. The amount of binding protein bound to the duplex DNA is compared before and after adding a test molecule. Comparison of the amount of binding protein bound to the duplex DNA before and after adding a test molecule can be accomplished, for example, using a gel band-shift assay or a filter-binding assay.

In the method of the present invention a number of DNA:protein interactions may be used for screening purposes. In one embodiment, the DNA screening sequence is from the HSV origin of replication and the binding protein is UL9. Exemplary HSV origin of replication screening sequences include SEQ ID NO:601, SEQ ID NO:602, SEQ ID NO:615, and SEQ ID NO:641.

Other DNA:protein interactions useful in the practice of the present invention include restriction endonucleases and their cognate DNA-binding sequences. These reactions are typically carried out in the absence of divalent cations.

In another embodiment, the invention includes a method of identifying test sequences in duplex DNA to which binding of a test molecule is most preferred. In this method a mixture of duplex DNA test oligonucleotides is constructed, where each oligonucleotide has a screening sequence adjacent a test sequence as described above. The test oligonucleotides of the mixture typically contain different test sequences.

A test molecule, to be screened, is added to a test reaction composed of (a) the DNA binding protein, and (b) the duplex DNA test oligonucleotide mixture. The molecule is incubated in the test reaction for a period sufficient to permit binding of the compound being tested to test sequences in the duplex DNA. Test oligonucleotides are separated from test oligonucleotides bound to binding protein

The test oligonucleotides can be separated from test oligonucleotides bound to protein by, for example, passing the test reaction through a filter, where the filter is capable of capturing DNA:protein complexes but not DNA that is free of protein. One filter type useful in the practice of the present invention is the nitrocellulose filter.

The separated test oligonucleotides are then amplified. These amplified test oligonucleotides are then recycled through the screening steps of the assay in order to obtain a desired degree of selection. The amplified test oligonucleotides are isolated and sequenced.

Exemplary test sequences include sequences selected from the group of 256 possible four base sequences composed of A, G, C and T. Further examples of desirable test sequences include test sequences derived from the sequences presented as SEQ ID NO:1 to SEQ ID NO:600.

The amplification step in the method may be accomplished by polymerase chain reaction or other methods of amplification, including, cloning and subsequent *in vivo* amplification of the cloning vector containing the sequences of interest.

These and other objects and features of the invention will be more fully appreciated when the following detailed description of the invention is read in conjunction with the accompanying drawings.

Brief Description of the Figures

Figure 1A illustrates a DNA-binding protein binding to a screening sequence. Figures 1B and 1C illustrate how a DNA-binding protein may be displaced or hindered in binding by a small molecule by two different mechanisms: because of stearic hinderance (1B) or because of conformational (allosteric) changes induced in the DNA by a small molecule (1C).

Figure 2 illustrates an assay for detecting inhibitory molecules based on their ability to preferentially hinder the binding of a DNA-binding protein to its binding site. Protein (O) is displaced from DNA (/) in the presence of inhibitor (X). Two alternative capture/detection systems are illustrated, the capture and detection of unbound DNA or the capture and detection of DNA:protein complexes.

Figure 3 shows a DNA-binding protein that is able to protect a biotin moiety, covalently attached to an

oligonucleotide sequence, from being recognized by streptavidin when a protein is bound to the DNA.

Figure 4 shows the incorporation of biotin and digoxigenin into a typical oligonucleotide molecule for use in the assay of the present invention. The oligonucleotide contains the binding sequence (*i.e.*, the screening sequence) of the UL9 protein, which is underlined, and test sequences flanking the screening sequence. Figure 4 also shows the preparation of double-stranded oligonucleotides end-labeled with either digoxigenin or ^{32}P.

Figure 5 shows a series of sequences that have been tested in the assay of the present invention for the binding of sequence-specific small molecules.

Figure 6 outlines the clonings, into an expression vector, of a truncated form of the UL9 protein (UL9-COOH) which retains its sequence-specific DNA-binding ability.

Figure 7 shows the pVL1393 baculovirus vector containing the full length UL9 protein coding sequence.

Figure 8 is a photograph of a SDS-polyacrylamide gel showing (i) the purified UL9-COOH/glutathione-S-transferase fusion protein and (ii) the UL9-COOH polypeptide.

Figure 9 presents data demonstrating the effect on UL9-COOH binding of alterations in the test sequences that flank the UL9 screening sequence.

Figure 10A shows the effect of the addition of several concentrations of distamycin A to DNA:protein assay reactions utilizing different test sequences. Figure 10B shows the effect of the addition of actinomycin D to DNA:protein assay reactions utilizing different test sequences. Figure 10C shows the effect of the addition of Doxorubicin to DNA:protein assay reactions utilizing different test sequences.

Figure 11A illustrates a DNA capture system of the present invention utilizing biotin and streptavidin coated magnetic beads. The presence of the DNA is detected using an alkaline-phosphatase substrate that yields a chemiluminescent product. Figure 11B shows a similar reaction using biotin coated agarose beads that are conjugated to streptavidin, that in turn is conjugated to the captured DNA.

Figure 12 demonstrates a test matrix based on DNA:protein-binding data.

Figure 13 lists the top strands (5'-3') of all the possible four base pair sequences that could be used as a defined set of ordered test sequences in the assay.

Figure 14A lists the top strands (5'-3') of all the possible four base pair sequences that have the same base composition as the sequence 5'-GATC-3'. This is another example of a defined, ordered set of sequences that could be tested in the assay. Figure 14B presents the general sequence of a test oligonucleotide (SEQ ID NO:617), where XXXX is the test sequence and N = A,G,C, or T.

Figure 15 shows the results of 4 duplicate experiments in which the binding activity of distamycin was tested with all possible (256) four base pair sequences. The oligonucleotides are ranked from 1 to 256 (column 1, "rank") based on their average rank from the four experiments (column 13, "ave. rank"). (rank is shown in the first column of the chart).

Figure 16 shows the average ranks (Figure 15) plotted against the ideal ranks 1 to 256.

Figure 17 shows the average r% scores (Figure 15) plotted against the rank of 1 to 256.

Figure 18 shows the results of eight experiments with actinomycin D. The r% scores and rank are shown for each of the 256 oligonucleotides.

Figure 19 shows the average r% versus rank, by average rank (data from Figure 18).

Figure 20 shows the ideal and average ranks for each of the 256 oligonucleotides.

Figure 21 shows the results of a position analysis for actinomycin D preference.

Figure 22 presents the data for a dinucleotide analysis of actinomycin D binding preference.

Figure 23 graphically displays the results presented in Figure 22.

Figure 24 graphically displays the data presented in Figure 22, where the data are combined in a combined bar chart so that the cumulative results for any dinucleotide pair are tabulated in a single bar.

Figure 25 shows the top strands of 16 possible duplex DNA target sites for binding bis-distamycins.

Figure 26 shows examples of bis-distamycin target sequences for bis-distamycins with internal flexible and/or variable length linkers targeted to sites comprised of two TTCC sequences, where N is any base.

Figures 27A to 27H show sample oligonucleotides for competition binding studies using the assay of the present invention.

Figure 28 shows the DNA sequences of the HIV pro-viral promoter region. Several transcription factor binding sites are marked.

Figures 29A to 29D illustrate sample test oligonucleotides for use in the polymerase chain reaction based selection technique of the present invention. In Figure 29A, X is the number of bases that comprise the test site.

Figure 30 illustrates a sample test oligonucleotide for use in the assay of the present invention, where the test oligonucleotide employs several different DNA:protein interaction systems.

Figure 31 illustrates the results of screening a selected test sequence with a single DNA:protein interaction system. In the figure, the test site is shown in bold, the potential binding site for the test molecule is underlined.

Figure 32 illustrates the results of screening the same selected test sequence as shown in Figure 31, but using a different single DNA:protein interaction system. In the figure, the test site is shown in bold, the potential binding site for the test molecule is underlined.

Detailed Description of the Invention

I. Definitions:

Adjacent is used to describe the distance relationship between two neighboring sites. Adjacent sites are 20 or less bp apart, and can be separated by any fewer number of bases including the situation where the sites are immediately abutting one another. "Flanking" is a synonym for adjacent.

Bound DNA, as used in this disclosure, refers to the DNA that is bound by the protein used in the assay (*e.g.*, a test oligonucleotide containing the UL9 binding sequence bound to the UL9 protein.

Coding sequences or coding regions are DNA sequences that code for RNA transcripts, unless specified otherwise.

Dissociation is the process by which two molecules cease to interact: the process occurs at a fixed average rate under specific physical conditions.

Functional binding is the noncovalent association of a protein or small molecule to the DNA molecule. In one embodiment of the assay of the present invention the functional binding of the UL9 protein to a screening sequence (*i.e.*, its cognate DNA binding site) has

been evaluated using filter binding or gel band-shift experiments.

Half-life is herein defined as the time required for one-half of the associated complexes, *e.g.*, DNA:protein complexes, to dissociate.

Heteropolymers are molecules comprised of at least two different subunits, each representing a different type or class of molecule. The covalent coupling of different subunits, such as, DNA-binding molecules or portions of DNA-binding molecules, results in the formation of a heteropolymer: for example, the coupling of a non-intercalating homopolymeric DNA-binding molecule, such as distamycin, to an intercalating drug, such as daunomycin. Likewise, the coupling of netropsin, which is essentially a molecular subunit of distamycin, to daunomycin would also be a heteropolymer. As a further example, the coupling of distamycin, netropsin, or daunomycin to a DNA-binding homopolymer, such as a triplex-forming oligonucleotide, would result in a heteropolymer.

Homopolymers are molecules that are comprised of a repeating subunit of the same type or class. Two examples of duplex DNA-binding homopolymers are as follows: (i) triplex-forming oligonucleotides or oligonucleotide analogs, which are composed of repeating subunits of nucleotides or nucleotide analogs, and (ii) oligopeptides, which are composed of repeating subunits linked by peptide bonds (*e.g.*, distamycin, netropsin).

Sequence-preferential binding refers to DNA binding molecules that generally bind DNA but that show preference for binding to some DNA sequences over others. Sequence-preferential binding is typified by several of the small molecules tested in the present disclosure, *e.g.*, distamycin. Sequence-preferential and sequence-specific binding can be evaluated using a

test matrix such as is presented in Figure 12. For a given DNA-binding molecule, there are a spectrum of differential affinities for different DNA sequences ranging from non-sequence-specific (no detectable preference) to sequence preferential to absolute sequence specificity (*i.e.*, the recognition of only a single sequence among all possible sequences, as is the case with many restriction endonucleases).

Sequence-specific binding refers to DNA binding molecules which have a strong DNA sequence binding preference. For example, the following demonstrate typical sequence-specific DNA-binding: (i) multimers (heteropolymers and homopolymers) of the present invention (*e.g.*, Section IV.E.1, Multimerization; Example 13), and (ii) restriction enzymes and the proteins listed in Table IV.

Screening sequence is the DNA sequence that defines the cognate binding site for the DNA binding protein: in the case of UL9, the screening sequence can, for example, be SEQ ID NO:601.

Small molecules are desirable as therapeutics for several reasons related to drug delivery, including the following: (i) they are commonly less than 10 K molecular weight; (ii) they are more likely to be permeable to cells; (iii) unlike peptides or oligonucleotides, they are less susceptible to degradation by many cellular mechanisms; and, (iv) they are not as apt to elicit an immune response. Many pharmaceutical companies have extensive libraries of chemical and/or biological mixtures, often fungal, bacterial, or algal extracts, that would be desirable to screen with the assay of the present invention. Small molecules may be either biological or synthetic organic compounds, or even inorganic compounds (*i.e.*, cisplatin).

Test sequence is a DNA sequence adjacent the screening sequence. The assay of the present invention screens for molecules that, when bound to the test sequence, affect the interaction of the DNA-binding protein with its cognate binding site (*i.e.*, the screening sequence). Test sequences can be placed adjacent either or both ends of the screening sequence. Typically, binding of molecules to the test sequence interferes with the binding of the DNA-binding protein to the screening sequence. However, some molecules binding to these sequences may have the reverse effect, causing an increased binding affinity of the DNA-binding protein to the screening sequence. Some molecules, even while binding in a sequence specific or sequence preferential manner, might have no effect in the assay. These molecules would not be detected in the assay.

Unbound DNA, as used in this disclosure, refers to the DNA that is not bound by the protein used in the assay (*i.e.*, in the examples of this disclosure, the UL9 protein).

II. The Assay.

One feature of the present invention is that it provides an assay to identify small molecules that will bind in a sequence-specific manner to medically significant DNA target sites. The assay facilitates the development of a new field of pharmaceuticals that operates by interfering with specific DNA functions, such as crucial DNA:protein interactions. A sensitive, well-controlled assay has been developmed (i) to detect DNA-binding molecules and (ii) to determine their sequence-specificity and affinity. The assay can be used to screen large biological and chemical libraries. For example, the assay will be used to detect sequence-

specific DNA-binding molecules in fermentation broths or extracts from various microorganisms.

Furthermore, another application for the assay is to determine the sequence specificity and relative affinities of known DNA-binding drugs (and other DNA-binding molecules) for different DNA sequences. Such drugs, which are currently used primarily as antibiotics or anticancer drugs, may have previously unidentified activities that make them strong candidates for therapeutics or therapeutic precursors in entirely different areas of medicine. The use of the assay to determine the sequence-binding preference of these known DNA-binding molecules enables the rational design of novel DNA-binding molecules with enhanced sequence-binding preference. The methods for designing and testing these novel DNA-binding molecules is described below.

The screening assay of the present invention is basically a competition assay that is designed to test the ability of a test molecule to compete with a DNA-binding protein for binding to a short, synthetic, double-stranded oligodeoxynucleotide that contains the recognition sequence for the DNA-binding protein flanked on either or both sides by a variable test site. The variable test site may contain any DNA sequence that provides a reasonable recognition sequence for a DNA-binding test molecule. Molecules that bind to the test site alter the binding characteristics of the protein in a manner that can be readily detected. The extent to which such molecules are able to alter the binding characteristics of the protein is likely to be directly proportional to the affinity of the test molecule for the DNA test site. The relative affinity of a given molecule for different oligonucleotide sequences at the test site (*i.e.*, test sequences) can be

established by examining the molecule's effect on the DNA:protein interaction using each of the test sequences.

The assay can be used to test specific target sequences and to identify novel DNA-binding molecules. Also, the assay provides a means for the determination of the high affinity DNA binding sites for a given DNA-binding molecule, thus facilitating the identification of specific target sequences.

A. <u>General Considerations</u>.

The assay of the present invention has been designed for detecting test molecules or compounds that affect the rate of transfer of a specific DNA molecule from one protein molecule to another identical protein in solution.

A mixture of DNA and protein is prepared in solution. The concentration of protein is in excess to the concentration of the DNA so that virtually all of the DNA is found in DNA:protein complexes. The DNA is a double-stranded oligonucleotide that contains the recognition sequence for a specific DNA-binding protein (*i.e.*, the screening sequence). The protein used in the assay contains a DNA-binding domain that is specific for binding to the sequence within the oligonucleotide. The physical conditions of the solution (*e.g.*, pH, salt concentration, temperature) are adjusted such that the half-life of the complex is amenable to performing the assay (optimally a half-life of 5-120 minutes), preferably in a range that is close to normal physiological conditions.

As one DNA:protein complex dissociates, the released DNA rapidly reforms a complex with another protein in solution. Since the protein is in excess to the DNA, dissociations of one complex always result in

the rapid reassociation of the DNA into another DNA:protein complex. At equilibrium, very few DNA molecules will be unbound. If the unbound DNA is the component of the system that is measured, the minimum background of the assay is the amount of unbound DNA observed during any given measurable time period. If the capture/detection system used for capturing the unbound DNA is irreversible, the brevity of the observation period (the length of time used to capture the unbound DNA) and the sensitivity of the detection system define the lower limits of background DNA.

Figure 1 illustrates how (i) such a protein can be displaced from its cognate binding site, (ii) a protein can be prevented from binding its cognate binding site, and (iii) how the kinetics of the DNA:protein interaction can be altered. In each case, the binding site for the test molecule is located at a site flanking the recognition sequence for the DNA-binding protein (Figure 1A). One mechanism is stearic hinderance of protein binding by a small molecule (competitive inhibition; Figure 1B). Alternatively, a molecule may interfere with a DNA:protein binding interaction by inducing a conformational change in the DNA (allosteric interference, noncompetitive inhibition; Figure 1C). In either event, if a test molecule that binds the oligonucleotide hinders binding of the protein, even transiently, the rate of transfer of DNA from one protein to another will be decreased. This will result in a net increase in the amount of unbound DNA and a net decrease in the amount of protein-bound DNA. In other words, an increase in the amount of unbound DNA or a decrease in the amount of bound DNA indicates the presence of an inhibitor, regardless of the mechanism of inhibition (competitive or noncompetitive).

Alternatively, molecules may be isolated that, when bound to the DNA, cause an increased affinity of the DNA-binding protein for its cognate binding site. In this case, the assay control samples (no drug added) are adjusted to less than 100% DNA:protein complex so that the increase in binding can be detected. The amount of unbound DNA (observed during a given measurable time period after the addition of the molecule) will decrease and the amount of bound DNA will increase in the reaction mixture as detected by the capture/detection system described in Section II.

B. <u>Choosing and Testing an Appropriate DNA-Binding Protein</u>.

Experiments performed in support of the present invention have defined an approach for identifying molecules having sequence-preferential DNA-binding. In this approach small molecules binding to sequences adjacent the cognate binding sequence can inhibit the protein/cognate DNA interaction. This assay has been designed to use a single DNA:protein interaction to screen for sequence-specific or sequence-preferential DNA-binding molecules that recognize virtually any sequence.

While DNA-binding recognition sites are usually quite small (4-17 bp), the sequence that is protected by the binding protein is larger (usually 5 bp or more on either side of the recognition sequence -- as detected by DNAase I protection (Galas, *et al.*) or methylation interference (Siebenlist, *et al.*).

Experiments performed in support of the present invention demonstrated that a single protein and its cognate DNA-binding sequence can be used to assay virtually any DNA sequence by placing a sequence of interest adjacent to the cognate site: a small mole-

cule bound to the adjacent site can be detected by alterations in the binding characteristics of the protein to its cognate site. Such alterations might occur by either stearic hindrance (which would cause the dissociation of the protein) or induced conformational changes in the recognition sequence for the protein (which may cause either enhanced binding or, more likely, decreased binding of the protein to its cognate site).

1. Criteria for Choosing an Appropriate DNA-Binding Protein.

There are several considerations involved in choosing DNA:protein complexes that can be employed in the assay of the present invention including:

a.) The half-life of the DNA:protein complex should be short enough to accomplish the assay in a reasonable amount of time. The interactions of some proteins with their cognate binding sites in DNA can be measured in days not minutes: such tightly bound complexes would inconveniently lengthen the period of time it takes to perform the assay.

b.) The half-life of the complex should be long enough to allow the measurement of unbound DNA in a reasonable amount of time. For example, the level of free DNA is dictated by the ratio between the time needed to measure free DNA and the amount of free DNA that occurs naturally due to the dissociation of the complex during the measurement time period.

In view of the above two considerations, practical useful DNA:protein half-lives fall in the range of approximately two minutes to several days: shorter half-lives may be accommodated by faster equipment and longer half-lives may be accommodated by destabilizing the binding conditions for the assay.

c.) A further consideration is that the kinetic interactions of the DNA:protein complex is relatively insensitive to the nucleotide sequences flanking the recognition sequence. The affinity of DNA-binding proteins may be affected by differences in the sequences adjacent to the recognition sequence. If the half-life of the complex is affected by the flanking sequence, the analysis of comparative binding data between different flanking oligonucleotide sequences becomes difficult but is not impossible.

2) <u>Testing DNA:Protein Interactions for Use in the Assay</u>.

a.) <u>Other DNA:Protein Interactions Useful in the Method of the Present Invention</u>. There are many known DNA:protein interactions that may be useful in the practice of the present invention, including (i) the DNA protein interactions listed in Table IV, (ii) bacterial, yeast, and phage systems such as lambda o_L-o_R/cro, and (iii) modified restriction enzyme systems (*e.g.*, protein binding in the absence of divalent cations, see Section IV). Any protein that binds to a specific recognition sequence may be useful in the present invention. One constraining factor is the effect of the immediately adjacent sequences (the test sequences) on the affinity of the protein for its recognition sequence. DNA:protein interactions in which there is little or no effect of the test sequences on the affinity of the protein for its cognate site are preferable for use in the described assay; however, DNA:protein interactions that exhibit test-sequence-dependent differential binding may still be useful if algorithms that compensate for the differential affinity are applied to the analysis of data. In general, the effect of flanking sequence composition on

the binding of the protein is likely to be correlated to the length of the recognition sequence for the DNA-binding protein. That is, the kinetics of binding for proteins with shorter recognition sequences are more likely to suffer from flanking sequence effects, while the kinetics of binding for proteins with longer recognition sequences are more likely to not be affected by flanking sequence composition. The present disclosure provides methods and guidance for testing the usefulness of such DNA:protein interactions, in the screening assay.

b.) <u>The Use of UL9 Proteins in the Practice of the Present Invention</u>.

Experiments performed in support of the present invention have identified a DNA:protein interaction that is particularly useful for the above described assay: the Herpes Simplex Virus (HSV) UL9 protein that binds the HSV origin of replication (*oriS*). The UL9 protein has fairly stringent sequence specificity. There appear to be three binding sites for UL9 in *oriS*, SEQ ID NO:601, SEQ ID NO:602 and SEQ ID NO:615 (Elias, *et al.*; Stow, *et al.*). One sequence (SEQ ID NO:601) binds with at least 10-fold higher affinity than the second sequence (SEQ ID NO:602): the embodiments described below use the higher affinity binding site (SEQ ID NO:601). Another useful UL9-binding site, alibi a lower affinity binding site, SEQ ID NO:641, has also been identified.

DNA:protein association reactions are performed in solution. The DNA:protein complexes can be separated from free DNA by any of several methods. One particularly useful method for the initial study of DNA:protein interactions has been visualization of binding results using band shift gels (Example 3A). In this method DNA:protein binding reactions are applied to

polyacrylamide/TBE gels and the labelled complexes and free labeled DNA are separated electrophoretically. These gels are fixed, dried, and exposed to X-ray film. The resulting autoradiograms are examined for the amount of free probe that is migrating separately from the DNA:protein complex. These assays include (i) a lane containing only free labeled probe, and (ii) a lane where the sample is labeled probe in the presence of a large excess of binding protein. The band shift assays allow visualization of the ratios between DNA:protein complexes and free probe. However, they are less accurate than filter binding assays for rate-determining experiments due to the lag time between loading the gel and electrophoretic separation of the components.

The filter binding method is particularly useful in determining the half-life for oligonucleotide:-protein complexes (Example 3B). In the filter binding assay, DNA:protein complexes are retained on a filter while free DNA passes through the filter. This assay method is more accurate for half-life determinations because the separation of DNA:protein complexes from free probe is very rapid. The disadvantage of filter binding is that the nature of the DNA:protein complex cannot be directly visualized. So if, for example, the competing molecule was also a protein competing for the binding of a site on the DNA molecule, filter binding assays cannot differentiate between the binding of the two proteins nor yield information about whether one or both proteins are binding.

C. <u>Preparation of Full Length UL9 and UL9-COOH Polypeptides</u>.

UL9 protein has been prepared by a number of recombinant techniques (Example 2). The full length

UL9 protein has been prepared from baculovirus infected insect cultures (Example 3A, B, and C). Further, a portion of the UL9 protein that contains the DNA-binding domain (UL9-COOH) has been cloned into a bacterial expression vector and produced by bacterial cells (Example 3D and E). The DNA-binding domain of UL9 is contained within the C-terminal 317 amino acids of the protein (Weir, *et al.*). The UL9-COOH polypeptide was inserted into the expression vector in-frame with the glutathione-S-transferase (gst) protein. The gst/UL9 fusion protein was purified using affinity chromatography (Example 3E). The vector also contained a thrombin cleavage site at the junction of the two polypeptides. Therefore, once the fusion protein was isolated (Figure 8, lane 2) it was treated with thrombin, cleaving the UL9-COOH/ gst fusion protein from the gst polypeptide (Figure 8, lane 3). The UL9-COOH-gst fusion polypeptide was obtained at a protein purity of greater than 95% as determined using Coomassie staining.

Other hybrid proteins can be utilized to prepare DNA-binding proteins of interest. For example, fusing a DNA-binding protein coding sequence in-frame with a sequence encoding the thrombin site and also in-frame with the β-galactoside coding sequence. Such hybrid proteins can be isolated by affinity or immunoaffinity columns (Maniatis, *et al.*; Pierce, Rockford IL). Further, DNA-binding proteins can be isolated by affinity chromatography based on their ability to interact with their cognate DNA binding site. For example, the UL9 DNA-binding site (SEQ ID NO:601) can be covalently linked to a solid support (*e.g.*, CnBr-activated Sepharose 4B beads, Pharmacia, Piscataway NJ), extracts passed over the support, the support washed, and the DNA-binding then isolated from the

support with a salt gradient (Kadonaga). Alternatively, other expression systems in bacteria, yeast, insect cells or mammalian cells can be used to express adequate levels of a DNA-binding protein for use in this assay.

The results presented below in regard to the DNA-binding ability of the truncated UL9 protein suggest that full length DNA-binding proteins are not required for the DNA:protein assay of the present invention: only a portion of the protein containing the cognate site recognition function may be required. The portion of a DNA-binding protein required for DNA-binding can be evaluated using a functional binding assay (Example 4A). The rate of dissociation can be evaluated (Example 4B) and compared to that of the full length DNA-binding protein. However, any DNA-binding peptide, truncated or full length, may be used in the assay if it meets the criteria outlined in Section II.B.1, "Criteria for choosing an appropriate DNA-binding protein". This remains true whether or not the truncated form of the DNA-binding protein has the same affinity as the full length DNA-binding protein.

D. <u>Functional Binding and Rate of Dissociation</u>.

The full length UL9 and purified UL9-COOH proteins were tested for functional activity in "band shift" assays (see Example 4A). The buffer conditions were optimized for DNA:protein-binding (Example 4C) using the UL9-COOH polypeptide. These DNA-binding conditions also worked well for the full-length UL9 protein. Radiolabeled oligonucleotides (SEQ ID NO:614) that contained the 11 bp UL9 DNA-binding recognition sequence (SEQ ID NO:601) were mixed with each UL9 protein in appropriate binding buffer. The reactions were incubated at room temperature for 10 minutes (binding

occurs in less than 2 minutes) and the products were separated electrophoretically on non-denaturing polyacrylamide gels (Example 4A).

The degree of DNA:protein-binding could be determined from the ratio of labeled probe present in DNA:protein complexes versus that present as free probe. This ratio was typically determined by optical scanning of autoradiograms and comparison of band intensities. Other standard methods may be used as well for this determination, such as scintillation counting of excised bands. The UL9-COOH polypeptide and the full length UL9 polypeptide, in their respective buffer conditions, bound the target oligonucleotide equally well.

The rate of dissociation was determined using competition assays. An excess of unlabelled oligonucleotide that contained the UL9 binding site was added to each reaction. This unlabelled oligonucleotide acts as a specific inhibitor, capturing the UL9 protein as it dissociates from the labelled oligonucleotide (Example 4B). The dissociation rate, as determined by a band-shift assay, for both full length UL9 and UL9-COOH was approximately 4 hours at 4°C or approximately 10 minutes at room temperature. Neither non-specific oligonucleotides (a 10,000-fold excess) nor sheared herring sperm DNA (a 100,000-fold excess) competed for binding with the oligonucleotide containing the UL9 binding site.

E. *oriS* Flanking Sequence Variation.

As mentioned above, one feature of a DNA:protein-binding system to be used in the assay of the present invention is that the DNA:protein interaction is not affected by the nucleotide sequence of the regions adjacent the DNA-binding site. The sensitivity of any

DNA:protein-binding reaction to the composition of the flanking sequences can be evaluated by the functional binding assay and dissociation assay described above.

To test the effect of flanking sequence variation on UL9 binding to the *oriS* SEQ ID NO:601 sequences oligonucleotides were constructed with 20-30 different sequences (*i.e.*, the test sequences) flanking the 5' and 3' sides of the UL9 binding site. Further, oligonucleotides were constructed with point mutations at several positions within the UL9 binding site. Most point mutations within the binding site destroyed recognition. Several changes did not destroy recognition and these include variations at sites that differ between the UL9 binding sites (SEQ ID NO:601, SEQ ID NO:602, SEQ ID NO:615 and SEQ ID NO:641): the second UL9 binding site (SEQ ID NO:602) shows a ten-fold decrease in UL9:DNA binding affinity (Elias, *et al.*) relative to the first (SEQ ID NO:601). On the other hand, sequence variation at the test site (also called the test sequence), adjacent to the screening site (Figure 5, Example 5), had virtually no effect on binding or the rate of dissociation.

The results demonstrating that the nucleotide sequence in the test site, which flanks the screening site, has no effect on the kinetics of UL9 binding in any of the oligonucleotides tested is a striking result. This allows the direct comparison of the effect of a DNA-binding molecule on test oligonucleotides that contain different test sequences. Since the only difference between test oligonucleotides is the difference in nucleotide sequence at the test site(s), and since the nucleotide sequence at the test site has no effect on UL9 binding, any differential effect observed between the two test oligonucleotides in response to a DNA-binding molecule <u>must</u> be due solely

to the differential interaction of the DNA-binding molecule with the test sequence(s). In this manner, the insensitivity of UL9 to the test sequences flanking the UL9 binding site greatly facilitates the interpretation of results. Each test oligonucleotide acts as a control sample for all other test oligonucleotides. This is particularly true when ordered sets of test sequences are tested (*e.g.*, testing all 256 four base pair sequences (Figure 13) for binding to a single drug).

Taken together the above experiments support that the UL9-COOH polypeptide binds the SEQ ID NO:601 sequence with (i) appropriate strength, (ii) an acceptable dissociation time, and (iii) indifference to the nucleotide sequences flanking the screening site. These features suggested that the UL9/*oriS* system could provide a versatile assay for detection of small molecule/DNA-binding involving any number of specific nucleotide sequences.

The above-described experiment can be used to screen other DNA:protein interactions to determine their usefulness in the present assay.

F. <u>Small Molecules as Sequence-Specific Competitive Inhibitors</u>.

To test the utility of the present assay system several small molecules that have sequence-binding preferences (*i.e.*, a preference for AT-rich versus GC-rich sequences) have been tested.

Distamycin A binds relatively weakly to DNA ($K_A = 2 \times 10^5\ M^{-1}$) with a preference for non-alternating AT-rich sequences (Jain, *et al.*; Sobell; Sobell, *et al.*). Actinomycin D binds DNA more strongly ($K_A = 7.6 \times 10^{-7}\ M^{-1}$) than Distamycin A and has been reported to have a relatively strong preference for the dinucleotide se-

quence dGdC (Luck, *et al.*; Zimmer; Wartel). Each of these molecules poses a stringent test for the assay. Distamycin A tests the sensitivity of the assay because of its relatively weak binding. Actinomycin D challenges the ability to utilize flanking sequences since the UL9 recognition sequence contains a dGdC dinucleotide: therefore, it might be anticipated that all of the oligonuclectides, regardless of the test sequence flanking the assay site, might be equally affected by actinomycin D.

In addition, Doxorubicin, a known anti-cancer agent that binds DNA in a sequence-preferential manner (Chen, K-X, *et al.*), has been tested for preferential DNA sequence binding using the assay of the present invention.

Actinomycin D, Distamycin A, and Doxorubicin have been tested for their ability to preferentially inhibit the binding of UL9 to oligonucleotides containing different sequences flanking the UL9 binding site (Example 6, Figure 5). Furthermore, distamycin A and actinomycin D have been screened against all possible 256 4 bp DNA sequences. Binding assays were performed as described in Example 5. These studies were completed under conditions in which UL9 is in excess of the DNA (*i.e.*, most of the DNA is in DNA:protein complexes).

In the preliminary studies, distamycin A was tested with 5 different test sequences flanking the UL9 screening sequence: SEQ ID NO:605 to SEQ ID NO:609. The results shown in Figure 10A demonstrate that Distamycin A preferentially disrupts binding to the test sequences UL9 polyT, UL9 polyA and, to a lesser extent, UL9 ATAT. Figure 10A also shows the concentration dependence of the inhibitory effect of distamycin A: at 1 μM distamycin A most of the DNA:protein

complexes are intact (top band) with free probe appearing in the UL9 polyT and UL9 polyA lanes, and some free probe appearing in the UL9 ATAT lane; at 4 μM free probe can be seen in the UL9 polyT and UL9 polyA lanes; at 16 μM free probe can be seen in the UL9 polyT and UL9 polyA lanes; and at 40 μM the DNA:protein in the polyT, UL9 polyA and UL9 ATAT lanes are near completely disrupted while some DNA:protein complexes in the other lanes persist. These results were consistent with the reported preference of Distamycin A for non-alternating AT-rich sequences.

Actinomycin D was tested with 8 different test sequences flanking the UL9 screening sequence: SEQ ID NO:605 to SEQ ID NO:609, and SEQ ID NO:611 to SEQ ID NO:613. The results shown in Figure 10B demonstrate that actinomycin D preferentially disrupts the binding of UL9-COOH to the oligonucleotides UL9 CCCG (SEQ ID NO:605) and UL9 GGGC (SEQ ID NO:606). These oligonucleotides contain, respectively, three or five dGdC dinucleotides in addition to the dGdC dinucleotide within the UL9 recognition sequence. This result is consistent with the results described in the literature for Actinomycin D binding to the dinucleotide sequence dGdC. Apparently the presence of a potential preferred target site within the screening sequence (*oriS*, SEQ ID NO:601), as mentioned above, does not interfere with the function of the assay.

Doxorubicin was tested with 8 different test sequences flanking the UL9 screening sequence: SEQ ID NO:605 to SEQ ID NO:609, and SEQ ID NO:611 to SEQ ID NO:613. The results shown in Figure 10C demonstrate that Doxorubicin preferentially disrupts binding to oriEco3, the test sequence of which differs from oriEco2 by only one base (compare SEQ ID NO:612 and SEQ ID NO:613). Figure 10C also shows the concentration

dependence of the inhibitory effect of Doxorubicin: at 15 μM Doxorubicin, the UL9 binding to the screening sequence is strongly affected when oriEco3 is the test sequence, and more mildly affected when polyT, UL9 GGGC, or oriEco2 was the test sequence; and at 35 μM Doxorubicin most DNA:protein complexes are nearly completely disrupted, with UL9 polyT and UL9ATAT showing some DNA still complexed with protein. Also, effects similar to those observed at 15 μM were also observed using Doxorubicin at 150 nM, but at a later time point.

The feasibility studies performed with the limited set of test sequences, described above, provided evidence that the results of the assay are not inconsistent with the results reported in the literature. However, the screening of all possible 256 four basepair sequences, using the assay of the present invention, provides a much more extensive overview of the sequence preferences of distamycin A and actinomycin D.

The actual ranking of values obtained from the assay, for any given test compound, can be variable. A number of sequences can be clustered having similar affinity: although absolute rank might not be determinable, relative ranks can be determined.

The results obtained in the feasibility studies with both distamycin A and actinomycin D were corroborated by the results obtained in the screen of all 256 sequences. In other words, the rank of the oligonucleotides remained internally consistent in the larger screen. Further, the screens of distamycin A and actinomycin D both support the general hypotheses described in the literature: that is, distamycin A has a preference for binding AT-rich sequences while actinomycin D has a preference for binding GC-rich sequences. However, both drug screens of all possible 4

bp sequences revealed additional characteristics that have not been described in the literature.

Based on the data from 4 separate experiments (Examples 10 and 11; Figures 15, 16 and 17), consensus sequences can be derived for distamycin binding. One consensus sequence (Example 11) is relatively AT-rich, although the preference in the 4th base position is distinctly G or C. The other consensus sequence (Example 11) is relatively GC-rich, with some of the sequences having a 75% GC-content. As noted above, the assay data is consistent with distamycin binding data shown in the literature.

The ability of the assay to distinguish sequence binding preference using weak DNA-binding molecules with relatively poor sequence-specificity (such as distamycin A) is a stringent test of the assay. Accordingly, the present assay seems well-suited for the identification of molecules having better sequence specificity and/or higher sequence binding affinity. Further, the results demonstrate sequence preferential binding with the known anti-cancer drug Doxorubicin. This result indicates the assay may be useful for screening mixtures for molecules displaying similar characteristics that could be subsequently tested for anti-cancer activities as well as sequence-specific binding.

Other compounds that may be suitable for testing in the present DNA:protein system or for defining alternate DNA:protein systems include the following categories of DNA-binding molecules.

A first category of DNA-binding molecules includes non-intercalating major and minor groove DNA-binding molecules. For example, two major classes of major groove binding molecules are DNA-binding proteins (or peptides) and nucleic acids (or nucleic acid analogs

such as those with peptide or morpholino backbones) capable of forming triplex DNA. There are a number of non-intercalating minor groove DNA-binding molecules including, but not limited to the following: distamycin A, netropsin, mithramycin, chromomycin and oligomycin, which are used as antitumor agents and antibiotics; and synthetic antitumor agents such as berenil, phthalanilides, aromatic bisguanylhydrazones and bisquaternary ammonium heterocycles (for review, see Baguley, 1982). Non-intercalating DNA-binding molecules vary greatly in structure: for example, the netropsin-distamycin series are oligopeptides compared to the diarylamidines berenil and stilbamidine.

A second category of DNA-binding molecules includes intercalating DNA-binding molecules. Intercalating agents are an entirely different class of DNA-binding molecules that have been identified as antitumor therapeutics and include molecules such as daunomycin (Chaires, *et al.*) and nogalomycin (Fox, *et al.*, 1988) (see Remers, 1984).

A third category of DNA-binding molecules includes molecules that have both groove-binding and intercalating properties. DNA-binding molecules that have both intercalating and minor groove binding properties include actinomycin D (Goodisman, *et al.*), echinomycin (Fox, *et al.* 1990), triostin A (Wang, *et al.*), and luzopeptin (Fox, 1988). In general, these molecules have one or two planar polycyclic moieties and one or two cyclic oligopeptides. Luzopeptins, for instance, contain two substituted quinoline chromophores linked by a cyclic decadepsipeptide. They are closely related to the quinoxaline family, which includes echinomycin and triostin A, although they luzopeptins have ten amino acids in the cyclic peptide, while the quinoxaline family members have eight amino acids.

In addition to the major classes of DNA-binding molecules, there are also some small inorganic molecules, such as cobalt hexamine, which is known to induce Z-DNA formation in regions that contain repetitive GC sequences (Gessner, *et al.*). Another example is cisplatin, cis-diamminedichloroplatinum(II), which is a widely used anticancer therapeutic. Cisplatin forms a covalent intrastrand crosslink between the N7 atoms of adjacent guanosines (Rice, *et al.*).

Furthermore, there are a few molecules, such as calichemicin, that have unusual biochemical structures that do not fall in any of the major categories. Calichemicin is an antitumor antibiotic that cleaves DNA and is thought to recognize DNA sequences through carbohydrate moieties (Hawley, *et al.*). Several DNA-binding molecules, such as daunomycin, A447C, and cosmomycin B have sugar group, which may play a role in the recognition process.

Limited sequence preferences for some of the above drugs have been suggested: for example, echinomycin is thought to preferentially bind to the sequence (A/T)CGT (Fox, *et al.*). However, the absolute sequence preferences of the known DNA-binding drugs have never been demonstrated. Despite the large number of publications in this field, prior to the development of the assay described herein, no methods were available for determining sequence preferences among all possible binding sequences.

G. <u>Theoretical Considerations on the Concentration of Assay Components</u>.

There are two major components in the assay, the test oligonucleotide (*i.e.*, the test sequence) and the DNA-binding domain of UL9, which is described below. A number of theoretical considerations have been

employed in establishing the assay system. In one embodiment of the invention, the assay is used as a mass-screening assay: in this embodiment the smallest volumes and concentrations possible were desirable. Each assay typically uses about 0.1-0.5 ng DNA in a 15-20 μl reaction volume (approximately 0.3-1.5 nM). The protein concentration is in excess and can be varied to increase or decrease the sensitivity of the assay. In the simplest scenario (stearic hindrance), where the small molecule is acting as a competitive inhibitor and the ratio of DNA:protein and DNA-binding test molecule:DNA is 1:1, the system kinetics can be described by the following equations:

$$D + P \rightarrow D{:}P, \text{ where } k_{fp}/k_{bp} = K_{eq,p} = [D{:}P]/[D][P]$$

and

$$D + X \rightarrow D{:}X, \text{ where } k_{fx}/k_{bx} = K_{eq,x} = [D{:}X]/[D][X]$$

D = DNA, P = protein, X = DNA-binding molecule, k_{fp} and k_{fx} are the rates of the forward reaction for the DNA:protein interaction and DNA:drug interaction, respectively, and k_{bp} and k_{bx} are the rates of the backwards reactions for the respective interactions. Brackets, [], indicate molar concentration of the components.

In the assay, both the protein, P, and the DNA-binding molecule or drug, X, are competing for the DNA. If stearic hindrance is the mechanism of inhibition, the assumption can be made that the two molecules are competing for the same site. When the concentration of DNA equals the concentration of the DNA:drug or

DNA:protein complex, the equilibrium binding constant, K_{eq}, is equal to the reciprocal of the protein concentration (1/[P]). When all three components are mixed together, the relationship between the drug and the protein can be described as:

$$K_{eq,p} = z(K_{eq,x})$$

where "z" defines the difference in affinity for the DNA between P and X. For example, if z =4, then the affinity of the drug is 4-fold lower than the affinity of the protein for the DNA molecule. The concentration of X, therefore, must be 4-fold greater than the concentration of P, to compete equally for the DNA molecule. Thus, the equilibrium affinity constant of UL9 will define the minimum level of detection with respect to the concentration and/or affinity of the drug. Low affinity DNA-binding molecules will be detected only at high concentrations; likewise, high affinity molecules can be detected at relatively low concentrations. With certain test sequences, complete inhibition of UL9 binding at markedly lower concentrations than indicated by these analyses have been observed, probably indicating that certain sites among those chosen for feasibility studies have affinities higher than previously published. Note that relatively high concentrations of known drugs can be utilized for testing sequence specificity. In addition, the binding constant of UL9 can be readily lowered by altering the pH or salt concentration in the assay if it ever becomes desirable to screen for molecules that are found at low concentration (*e.g.*, in a fermentation broth or extract).

The system kinetic analysis becomes more complex if more than one protein or drug molecule is bound by

each DNA molecule. As an example, if UL9 binds as a dimer,

$$D + 2P \rightarrow DP_2$$

then the affinity constant becomes dependent on the square of the protein concentration:

$$K = [DP_2]/[D][P]^2$$

The same reasoning holds true for the DNA-binding test molecule, X; if,

$$D + 2X \rightarrow DX_2$$

then the affinity constant becomes dependent on the square of the protein concentration:

$$K = [DX_2]/[D][X]^2$$

Similarly, if the molar ratio of DNA to DNA-binding test molecule was 1:3, the affinity constant would be dependent on the cube of the drug concentration.

Experimentally, the ratio of molar components can be determined. Given the chemical equation:

$$xD + yP \rightarrow D_xP_y,$$

the affinity constant may be described as

$$K = [D_xP_y]/[D]^x[P]^y$$

where [] indicates concentration, D = DNA, P = protein, x = number of DNA molecules per DNA:protein complex, and y = number of protein molecules per DNA:protein

complex. By determining the ratio of DNA:protein complex to free DNA, one can solve for x and y:

if $x_{total} = x_{free} + x_{bound}$;

if a = the fraction of DNA that is free, then the fraction of DNA that is bound can be described as 1-a;

and if $x_{bound}:x_{free}$ (the ratio of DNA:protein complex to free DNA) is known for more than one DNA concentration. This is because the affinity constant should not vary at different DNA concentrations. Therefore,

$$K_{D:P,\ [D1]} = K_{D:P,\ [D2]}.$$

Substituting the right side of the equation above,

$$[D1_xP_y]/[D1]^x[P]^y = [D2_xP_y]/[D2]^x[P]^y.$$

Because the concentration of components in the assay can be varied and are known, the molar ratio of the components can be determined. Therefore, $[D1_xP_y]$ and $[D2_xP_y]$ can be described as $(1-a_1)[x_1]$ and $(1-a_2)[x_2]$, respectively, and [D1] and [D2] can be described as $(a_1)[x_1]$ and $(a_2)[x_2]$, respectively. [P] remains constant and is described as (y)-(y/x)(1-a)(x), where y is the total protein concentration and (y/x)(1-a)(x) is the protein complexed with DNA.

The system kinetic analyses become more complex if the inhibition is allosteric (non-competitive inhibition) rather than competition by stearic hindrance. Nonetheless, the probability that the relative effect of an inhibitor on different test sequences is due to its relative and differential affinity to the different test sequences is fairly high. This is particularly true in the assays in which all sequences within an ordered set (*e.g.*, possible sequences of a given length or all possible variations of a certain base composi-

tion and defined length) are tested. In short, if the effect of inhibition in the assay is particularly strong for a single sequence, then it is likely that the inhibitor binds that particular sequence with higher affinity than any of the other sequences. Furthermore, while it may be difficult to determine the absolute affinity of the inhibitor, the relative affinities have a high probability of being reasonably accurate. This information will be most useful in facilitating, for instance, the refinement of molecular modeling systems.

H. The Use of the Assay under Conditions of Very High Protein Concentration.

When the screening protein is added to the assay system at very high concentrations (*i.e.*, high enough to force binding to non-specific sites -- the protein binds to non-specific sites on the oligonucleotide as well as the screening sequence). This has been demonstrated using band shift gels: when serial dilutions are made of the protein and mixed with a fixed concentration of oligonucleotide, no binding (as seen by a band shift) is observed at very low dilutions (*e.g.*, 1:100,000), a single band shift is observed at moderate dilutions (*e.g.*, 1:100) and a smear, migrating higher than the single band observed at moderate dilutions, is observed at high concentrations of protein (*e.g.*, 1:10). The observation of a smear is indicative of a mixed population of complexes, all of which presumably have the screening protein binding to the screening sequence with high affinity, but in addition have a larger number of proteins bound with markedly lower affinity to other sites.

Some of the low affinity binding proteins ar likely bound to the test sequence. For example, when

using the UL9-based system, the low affinity binding proteins are likely UL9 or less likely glutathione-S-transferase: these are the only proteins in the assay mixture. These proteins are significantly more sensitive to interference by a molecule binding to the test sequence for two reasons. First, the interference is likely to be by direct stearic hinderance and does not rely on induced conformational changes in the DNA; secondly, the protein is a low affinity binding protein because the test site is not a cognate-binding sequence. In the case of UL9, the difference in affinity between the low affinity binding and the high affinity binding appears to be at least two orders of magnitude.

The filter binding assays capture more DNA:protein complexes when more protein is bound to the DNA. The relative results are accurate, but under moderate protein concentrations, not all of the bound DNA (as demonstrated by band shift assays) will bind to the filter unless there is more than one DNA:protein complex per oligonucleotide (*e.g.*, in the case of UL9, more than one UL9:DNA complex). This makes the assay exquisitely sensitive under conditions of high protein concentration. For instance, when actinomycin binds DNA at a test site under conditions where there is one DNA:UL9 complex per oligonucleotide, a preference for binding GC-rich oligonucleotides has been observed; under conditions of high protein concentration, where more than one DNA:UL9 complex is found per oligonucleotide, this binding preference is even more apparent. These results suggest that the effect of actinomycin D on a test site that is weakly bound by protein may be more readily detected than the effect of actinomycin D on the adjacent screening sequence. Therefore, employing high protein concentrations may increase the sensitivity of the assay.

III. Amplification-Based Selection Technique to Determine the Sequence Preferences of DNA-Binding Molecules.

A. Design of Test Oligonucleotides.

The above-described assay can be coupled to amplification methods (in one embodiment, polymerase chain reaction (Mullis, et *al.*; Mullis; Innis, et al.)) to achieve identification of the sequences to which binding of a test molecule is most preferred.

In this embodiment of the present invention, a double stranded test oligonucleotide is synthesized that contains the following elements:

(i) the binding site for a DNA-binding protein (for example, UL9), *i.e.*, the screening site,

(ii) adjacent the screening site, a test site composed of more than two base pairs and preferably less than 20 base pairs (most preferably 4-12 bases), and

(iii) means to isolate selected sequences for amplification, such as a sufficient number of bases flanking the test site sequences to function as priming sites for polymerase chain reaction amplification or restriction sites useful to facilitate cloning.

Priming sites can also be used as primer binding sites for dideoxy sequencing reactions and may contain restriction endonuclease cleavage sites to facilitate cloning manipulations.

The double-stranded test oligonucleotide can be generated by second-strand synthesis using a primer complementary to the priming site at the 3′ end of the top-strand of the test oligonucleotide. Alternatively, both strands can be generated by other means, such as chemical synthesis, and the double-stranded test oligonucleotides can be generated by hybridization of the strands.

An example of one such a test oligonucleotide is shown in Figure 29A (SEQ ID NO:630, SEQ ID NO:631 and SEQ ID NO:632). A specific example of a test oligonucleotide is shown in Figure 29B (SEQ ID NO:633), where X=4. All possible 256 four base pair sequences are represented at equimolar levels within the pool of oligonucleotides generated by this sequence design.

Another example of such a test oligonucleotide sequence is shown in Figure 29C (SEQ ID NO:634), for an 8 base pair test sequence. In this pool of mixed sequences, all possible 8 base pair sequences (4^8 = 65,536) are present in equimolar amounts.

A second set of test oligonucleotides may be constructed in which the test site is placed on the other side of the DNA-binding protein recognition site (*e.g.*, Figure 29D, SEQ ID NO:635).

For any single-stranded test oligonucleotide pool, the single-stranded molecules are annealed to a primer and the bottom strands are enzymatically synthesized by primer extension reactions. One advantage of using the assay/amplification PCR-cycling embodiment of the present invention is that it is convenient to work with larger test sequences in this embodiment. This protocol is geared to determining the highest affinity binding sequences and is not capable of determining the rank of all test sequences nor of identifying low affinity binding sites: such ranking can be determined by screening individual sequences as described above.

B. Applying the Assay to the Mixed Pools of Test Oligonucleotides.

Using double-stranded test oligonucleotides, such as those just described, the basic assay is performed essentially as described above (Section I): typically without the use of radioactive detection systems. As

previously discussed, a number of DNA:protein interactions may be used in this assay system. One example of such a system is the interaction of the DNA-binding domain of UL9 (or UL9-COOH) with its cognate recognition sequence.

In this embodiment of the present invention, UL9-COOH is added to the test oligonucleotide pool (for example, 256 four base pair sequences are represented at equimolar levels within the pool of oligonucleotides described above) in UL9 binding buffer. DNA-binding molecules are tested for the ability to differentially disrupt the binding of the UL9 DNA:protein complex by binding to the test sequence. After the addition of the test molecule or test mixture (*e.g.*, a fermentation broth or fungal extract), the assay mixture is incubated for a desired time, then passed through a nitrocellulose filter. DNA:protein (such as DNA:UL9) complexes are captured on the filter. DNA that is not bound by protein passes through the filter (*i.e.*, the filtrate) (step 1). The volume of the assay is adjusted to accommodate the amount required for the filtering process: that is, taking into consideration the losses incurred during the filtering process.

C. Amplification.

In one embodiment, the DNA present in the filtrate is amplified using the polymerase chain reaction (PCR) technology (Mullis; Mullis, *et al.*; Perkin Elmer-Cetus). An aliquot of the resulting PCR-amplified material is cycled through the DNA:protein binding assay again (step 2), then PCR-amplified again (step 3). Steps 1-3 are repeated several times using each subsequent filtrate. After each PCR amplification, part of the PCR-amplified material is retained for sequencing analysis. The result of the repeated

cyclings through the assay/amplification process is that the test oligonucleotide sequences that are amplified contain test sequences that are preferred binding sites for the test molecules. Through subsequent rounds of assay/amplification, these oligonucleotides are amplified to represent a larger and larger percent of the total population of amplified DNA molecules.

In addition to PCR, the DNA present in the filtrate can be amplified by other methods as well. For example, the DNA present in the filtrate can be cloned into a selected vector (such as, phage vectors, *e.g.*, lambda-based, or standard cloning vectors, *e.g.*, pBR322- or pUC-based). The cloned sequences are then transformed into an appropriate host organism in which the selected vector can replicate (for example, bacteria or yeast). The transformed host organism is cultured with concurrent amplification of the vectors containing the cloned sequences. The vectors are then isolated by standard procedures (Maniatis, *et al.*; Sambrook, *et al.*; Ausubel, *et al.*). Typically, the cloned sequences, originally obtained from the DNA filtrate, are obtained from the vector by restriction endonuclease digestion and size-fractionation (for example, electrophoretic separation of the digestion products followed by electroelution of the cloned sequences of interest) (Ausubel, *et al.*). These isolated amplified test oligonucleotide sequences can then be recycled through subsequent rounds of assay/amplification as described above.

In another embodiment, the oligonucleotide sequences present in the original DNA filtrate can be isolated, sequenced and amplified by *in vitro* synthesis of copies of the oligonucleotides.

D. Sequencing of Amplified DNA.

Samples from each cycle are sequenced using, for example, radio-labeled primers and dideoxy sequencing methodologies (Sanger) or the chemical methodologies outlined by Maxam and Gilbert. If the amplified sequences are not sufficiently resolved to obtain a unambiguous sequence information, then the DNA is further purified and sequenced. For example, the DNA is cleaved at the restriction endonuclease sites within the primer sequences and subcloned into a convenient sequencing vector, such as "BLUESCRIPT" (Stratagene, La Jolla, CA). The sequencing vectors carrying the amplified inserts are transformed into bacteria. The resulting cloned vectors are isolated and sequenced (in the case of "BLUESCRIPT," using the commercially available primers and protocols).

IV. Modifications of Test Oligonucleotides and other Useful DNA:Protein Interactions

One class of DNA:protein interactions that may be useful in the assay of the present invention is the restriction endonuclease:restriction site class of DNA:protein interactions. In the absence of divalent cations, restriction endonucleases bind DNA but have no enzymatic activity (cleavage of DNA does not take place without divalent cations). This allows the assay of the present invention to be performed using a restriction endonuclease with its cognate binding site as the screening sequence. The use of the restriction endonuclease:restriction site interaction as the basis of the present assay is described in greater detail in Section VI.B.4(c).

The test oligonucleotides of the present invention can be modified to contain two different DNA:protein screening systems, *i.e.*, two different screening se-

quences with their respective cognate binding proteins. In the assay described above, the UL9 screening sequence lies on one side of and immediately adjacent to the test sequence. A second screening sequence, such as, a restriction endonuclease recognition sequence (restriction site), can be introduced immediately adjacent to the other side of the test sequence.

Several restriction enzymes may recognize the same restriction site. These enzymes are not identical, however, in that the cleavage sites may be at the 5′ end, the center, or the 3′ end of the recognition sequence. For this reason, a restriction site that is recognized by more than one restriction enzyme may be incorporated adjacent to the test site. This allows a single pool of test oligonucleotides to be used in assays employing three different DNA:protein interactions: the screening sequence has the same sequence but the restriction endonuclease used in the assay system is different in each case. Using this method to design test oligonucleotides, the UL9 screening sequence may be placed on one side of a test sequence and a restriction site screening sequence (having three cognate binding proteins) may be placed on the other side of the test sequence. Such a test oligonucleotide construction allows 4 different DNA:protein assay interaction systems to be employed with a single pool of test sequences.

One example of test oligonucleotides using several different DNA:protein interaction systems are shown in Figure 30. The top strands of the pool of test oligonucleotides shown in Figure 30 have 6 base pair test sequences (NNNNNN) and represent synthetic pools of all possible 4096 test sequences. The remainder of the nucleotide sequence is fixed. The test oligonucleotides contain the UL9 recognition sequence, 5′-

CGTTCGCACTT-3′ (underlined) on one side of the test sequence and a restriction endonuclease binding sequence, 5′-GGTACC-3′ (bold), on the other side of the test site. The restriction endonuclease recognition sequence is recognized by the three different restriction endonucleases *Asp718*, *RsaI* and *KpnI*. In Figure 30 the UL9 binding site (screening sequence) is located 3′ of the test sequence: the UL9 binding site (screening sequence) can also be located 5′ of the test sequence.

The shorter sequences shown above the 5′ and 3′ ends of the test oligonucleotides are primer sequences useful for sequencing and PCR amplification. The primer sequences contain commonly used restriction endonuclease sites for the purpose of subcloning into sequencing vectors.

Performing the assay with two or more different protein/screening sequence systems allows the confirmation of putative high affinity binding between a test compound and specific test sequences.

Alternatively, since there is no assurance that a test molecule that binds the test sequence will have the same effect on protein binding at both adjacent flanking sequences, simultaneous use of both test systems may reduce the number of false negatives detected in an assay. For example, a test molecule that does not affect the binding of protein at one screening site but may effect the binding of a different protein at the other screening site.

V. Capture/Detection Systems.

As an alternative to the above described band shift gels and filter binding assays, the measurement of inhibitors can be monitored by measuring either the level of unbound DNA in the presence of test molecules or mixtures or the level of DNA:protein complex

remaining in the presence of test molecules or mixtures. Measurements may be made either at equilibrium or, in a kinetic assay, prior to the time at which equilibrium is reached. The type of measurement is likely to be dictated by practical factors, such as the length of time to equilibrium, which will be determined by both the kinetics of the DNA:protein interaction as well as the kinetics of the DNA:drug interaction. The results (*i.e.*, the detection of DNA-binding molecules and/or the determination of their sequence preferences) should not vary with the type of measurement taken (kinetic or equilibrium).

Figure 2 illustrates an assay for detecting inhibitory molecules based on their ability to preferentially hinder the binding of a DNA-binding protein. In the presence of an inhibitory molecule (X) the equilibrium between the DNA-binding protein and its binding site (screening sequence) is disrupted. The DNA-binding protein (O) is displaced from DNA (/) in the presence of inhibitor (X), the DNA free of protein or, alternatively, the DNA:protein complexes, can then be captured and detected.

For maximum sensitivity, unbound DNA and DNA:protein complexes should be sequestered from each other in an efficient and rapid manner. The method of DNA capture should allow for the rapid removal of the unbound DNA from he protein-rich mixture containing the DNA:protein complexes.

Even if the test molecules are specific in their interaction with DNA they may have relatively low affinity and they may also be weak binders of non-specific DNA or have non-specific interactions with DNA at low concentrations. In either case, their binding to DNA may only be transient, much like the transient binding of the protein in solution. Accordingly, one

feature of the assay is to take a molecular snapshot of the equilibrium state of a solution comprised of the test oligonucleotide DNA, the protein, and the inhibitory test molecule. In the presence of an inhibitor, the amount of DNA that is not bound to protein will be greater than in the absence of an inhibitor. Likewise, in the presence of an inhibitor, the amount of DNA that is bound to protein will be lesser than in the absence of an inhibitor.

Any method used to separate the DNA:protein complexes from unbound DNA, should be rapid, because when the capture system is applied to the solution (if the capture system is irreversible), the ratio of unbound DNA to DNA:protein complex will change at a predetermined rate, based purely on the off-rate of the DNA:protein complex. This step, therefore, determines the limits of background. Unlike the protein and inhibitor, the capture system should bind rapidly and tightly to the DNA or DNA:protein complex. The longer the capture system is left in contact with the entire mixture of unbound DNA and DNA:protein complexes in solution, the higher the background, regardless of the presence or absence of inhibitor.

Two exemplary capture systems are described below for use in the assay of the present invention. One capture system has been devised to capture unbound DNA (Section V.A). The other has been devised to capture DNA:protein complexes (Section V.B). Both systems are amenable to high throughput screening assays. The same detection methods (Section V.C) can be applied to molecules captured using either capture system.

A. Capture of Unbound DNA.

One capture system that has been developed in the course of experiments performed in support of the

present invention utilizes a streptavidin/biotin interaction for the rapid capture of unbound DNA from the protein-rich mixture, which includes unbound DNA, DNA:protein complexes, excess protein and the test molecules or test mixtures. Streptavidin binds with extremely high affinity to biotin ($K_d = 10^{-15}$M) (Chaiet, *et al.*; Green). Accordingly, two advantages of the streptavidin/biotin system are that binding between the two molecules can be rapid and the interaction is the strongest known non-covalent interaction.

In this detection system a biotin molecule is covalently attached in the oligonucleotide screening sequence (*i.e.*, the DNA-binding protein's binding site). This attachment is accomplished in such a manner that the binding of the DNA-binding protein to the DNA is not destroyed. Further, when the protein is bound to the biotinylated sequence, the protein prevents the binding of streptavidin to the biotin. In other words, the DNA-binding protein is able to protect the biotin from being recognized by the streptavidin. This DNA:protein interaction is illustrated in Figure 3.

The capture system is described herein for use with the UL9/*oriS* system described above. The following general testing principles can, however, be applied to analysis of other DNA:protein interactions. The usefulness of this system depends on the biophysical characteristics of the particular DNA:protein interaction.

1. <u>Modification of the Protein Recognition Sequence with Biotin</u>.

The recognition sequence for the binding of the UL9 (Koff, *et al.*) protein is underlined in Figure 4. Oligonucleotides were synthesized that contain the

UL9 binding site and site-specifically biotinylated a number of locations throughout the binding sequence (SEQ ID NO:614; Example 1, Figure 4). These biotinylated oligonucleotides were then used in band shift assays to determine the ability of the UL9 protein to bind to the oligonucleotide. These experiments using the biotinylated probe and a non-biotinylated probe as a control demonstrate that the presence of a biotin at the #8-T (biotinylated deoxyuridine) position of the bottom strand meets the requirements listed above: the presence of a biotin moiety at the #8 position of the bottom strand does not markedly affect the specificity of UL9 for the recognition site. Further, in the presence of bound UL9, streptavidin does not recognize the presence of the biotin moiety in the oligonucleotide. Biotinylation at other A or T positions did not have the two necessary characteristics (*i.e.*, UL9 binding and protection from streptavidin): biotinylation at the adenosine in position #8, of the top strand, prevented the binding of UL9; biotinylation of either adenosines or thymidines (top or bottom strand) at positions #3, #4, #10, or #11 all allowed binding of UL9, but in each case, streptavidin also was able to recognize the presence of the biotin moiety and thereby bind the oligonucleotide in the presence of UL9.

The above result (the ability of UL9 to bind to an oligonucleotide containing a biotin within the recognition sequence and to protect the biotin from streptavidin) was unexpected in that methylation interference data (Koff, *et al.*) suggest that methylation of the deoxyguanosine residues at positions #7 and #9 of the recognition sequence (on either side of the biotinylated deoxyuridine) blocks UL9 binding. In these methylation interference experiments, guanosines are methylated by dimethyl sulfate at the N^7 position,

which corresponds structurally to the 5-position of the pyrimidine ring at which the deoxyuridine is biotinylated. These moieties all protrude into the major groove of the DNA. The methylation interference data suggest that the #7 and #9 position deoxyguanosines are contact points for UL9, it was therefore unexpected that the presence of a biotin moiety between them would not interfere with binding.

The binding of the full length protein was relatively unaffected by the presence of a biotin at position #8 within the UL9 binding site. The rate of dissociation was similar for full length UL9 with both biotinylated and un-biotinylated oligonucleotides. However, the rate of dissociation of the truncated UL9-COOH polypeptide was faster with the biotinylated oligonucleotides than with non-biotinylated oligonucleotides (for non-biotinylated oligonucleotides the rate comparable to that of the full length protein with either DNA).

The binding conditions were optimized for UL9-COOH so that the half-life of the truncated UL9 from the biotinylated oligonucleotide was 5-10 minutes (optimized conditions are given in Example 4), a rate compatible with a mass screening assay. The use of multi-well plates to conduct the DNA:protein assay of the present invention is one approach to mass screening.

2. Capture of Site-Specific Biotinylated Oligonucleotides.

The streptavidin:biotin interaction can be employed in several different ways to remove unbound DNA from the solution containing the DNA, protein, and test molecule or mixture. Magnetic polystyrene or agarose beads, to which streptavidin is covalently

attached or attached through a covalently attached biotin, can be exposed to the solution for a brief period, then removed by use, respectively, of magnets or a filter mesh. Magnetic streptavidinated beads are currently the method of choice. Streptavidin has been used in many of these experiments, but avidin is equally useful.

An example of a second method for the removal of unbound DNA is to attach streptavidin to a filter by first linking biotin to the filter, binding streptavidin, then blocking nonspecific protein binding sites on the filter with a nonspecific protein such as albumin. The mixture is then passed through the filter, unbound DNA is captured and the bound DNA passes through the filter. This method can give high background due to partial retention of the DNA:protein complex on the filter.

One convenient method to sequester captured DNA is the use of streptavidin-conjugated superparamagnetic polystyrene beads as described in Example 7. These beads are added to the assay mixture to capture the unbound DNA. After capture of DNA, the beads can be retrieved by placing the reaction tubes in a magnetic rack, which sequesters the beads on the reaction chamber wall while the assay mixture is removed and the beads are washed. The captured DNA is then detected using one of several DNA detection systems, as described below.

Alternatively, avidin-coated agarose beads can be used. Biotinylated agarose beads (immobilized D-biotin, Pierce) are bound to avidin. Avidin, like streptavidin, has four binding sites for biotin. One of these binding sites is used to bind the avidin to the biotin that is coupled to the agarose beads via a 16 atom spacer arm: the other biotin binding sites

remain available. The beads are mixed with binding mixtures to capture biotinylated DNA (Example 7). Alternative methods (Harlow, *et al.*) to the bead capture methods just described include the following streptavidinated or avidinated supports: low-protein binding filters, or 96-well plates.

B. Capture of DNA:Protein Complexes.

The amount of DNA:protein complex remaining in the assay mixture in the presence of an inhibitory molecule can also be determined as a measure of the relative effect of the inhibitory molecule. A net decrease in the amount of DNA:protein complex in response to a test molecule is an indication of the presence of an inhibitor. DNA molecules that are bound to protein can be captured on nitrocellulose filters. Under low salt conditions, DNA that is not bound to protein freely passes through the filter. Thus, by passing the assay mixture rapidly through a nitrocellulose filter, the DNA:protein complexes and unbound DNA molecules can be rapidly separated. This has been accomplished on nitrocellulose discs using a vacuum filter apparatus or on slot blot or dot blot apparatuses (all of which are available from Schleicher and Schuell, Keene, NH). The assay mixture is applied to and rapidly passes through the wetted nitrocellulose under vacuum conditions. Any apparatus employing nitrocellulose filters or other filters capable of retaining protein while allowing free DNA to pass through the filter would be suitable for this system.

C. Detection Systems.

For either of the above capture methods, the amount of DNA that has been captured is quantitated. The method of quantitation depends on how the DNA has

been prepared. If the DNA is radioactively labelled, beads can be counted in a scintillation counter, or autoradiographs can be taken of dried gels or nitrocellulose filters. The amount of DNA has been quantitated in the latter case by a densitometer (Molecular Dynamics, Sunnyvale, CA); alternatively, filters or gels containing radiolabeled samples can be quantitated using a phosphoimager (Molecular Dynamics). Further, the captured DNA may be detected using a chemiluminescent or colorimetric detection system.

Radiolabelling and chemiluminescence (i) are very sensitive, allowing the detection of sub-femtomole quantities of oligonucleotide, and (ii) use well-established techniques. In the case of chemiluminescent detection, protocols have been devised to accommodate the requirements of a mass-screening assay. Non-isotopic DNA detection techniques have principally incorporated alkaline phosphatase as the detectable label given the ability of the enzyme to give a high turnover of substrate to product and the availability of substrates that yield chemiluminescent or colored products.

1. <u>Radioactive Labeling</u>.

Many of the experiments described above for UL9 DNA:protein-binding studies have made use of radiolabelled oligonucleotides. The techniques involved in radiolabelling of oligonucleotides have been discussed above. A specific activity of 10^8-10^9 dpm per μg DNA is routinely achieved using standard methods (*e.g.*, end-labeling the oligonucleotide with adenosine γ-[^{32}P]-5' triphosphate and T4 polynucleotide kinase). This level of specific activity allows small amounts of DNA to be measured either by autoradiography of gels or

filters exposed to film or by direct counting of samples in scintillation fluid.

2. Chemiluminescent Detection.

For chemiluminescent detection, digoxigenin-labelled oligonucleotides (Example 1) can be detected using the chemiluminescent detection system "SOUTHERN LIGHTS," developed by Tropix, Inc. (Bedord, MA). The detection system is diagrammed in Figures 11A and 11B. The technique can be applied to detect DNA that has been captured on either beads, filters, or in solution.

Alkaline phosphatase is coupled to the captured DNA without interfering with the capture system. To do this several methods, derived from commonly used ELISA (Harlow, *et al.*; Pierce, Rockford IL) techniques, can be employed. For example, an antigenic moiety is incorporated into the DNA at sites that will not interfere with (i) the DNA:protein interaction, (ii) the DNA:drug interaction, or (iii) the capture system. In the UL9 DNA:protein/biotin system the DNA has been end-labelled with digoxigenin-11-dUTP (dig-dUTP) and terminal transferase (Example 1, Figure 4). After the DNA was captured and removed from the DNA:protein mixture, an anti-digoxigenin-alkaline phosphatase conjugated antibody was then reacted (Boehringer Mannheim, Indianapolis IN) with the digoxigenin-containing oligonucleotide. The antigenic digoxigenin moiety was recognized by the antibody-enzyme conjugate. The presence of dig-dUTP altered neither the ability of UL9-COOH protein to bind the *oriS* (SEQ ID NO:601)-containing DNA nor the ability of streptavidin to bind the incorporated biotin.

Captured DNA was detected using the alkaline phosphatase-conjugated antibodies to digoxigenin as follows. One chemiluminescent substrate for alkaline

phosphatase is 3-(2'-spiroadamantane)-4-methoxy-4-(3"-phosphoryloxy) phenyl-1,2-dioxetane disodium salt (AMPPD) (Example 7). Dephosphorylation of AMPPD results in an unstable compound, which decomposes, releasing a prolonged, steady emission of light at 477 nm. Light measurement is very sensitive and can detect minute quantities of DNA (*e.g.*, 10^2-10^3 attomoles) (Example 7).

Colorimetric substrates for the alkaline phosphatase system have also been tested. While the colorimetric substrates are useable in the present assay system, use of the light emission system is more sensitive.

An alternative to the above biotin capture system is to use digoxigenin in place of biotin to modify the oligonucleotide at a site protected by the DNA-binding protein at the assay site: biotin is then used to replace the digoxigenin moieties in the above described detection system. In this arrangement the anti-digoxigenin antibody is used to capture the oligonucleotide probe when it is free of bound protein. Streptavidin conjugated to alkaline phosphatase is then used to detect the presence of captured oligonucleotides.

D. Alternative Methods for Detecting Molecules that Increase the Affinity of the DNA-Binding Protein for its Cognate Site.

In addition to identifying molecules or compounds that cause a decreased affinity of the DNA-binding protein for the screening sequence, molecules may be identified that increase the affinity of the protein for its cognate binding site. In this case, leaving the capture system for unbound DNA in contact with the assay for increasing amounts of time allows the establishment of a fixed half-life for the DNA:protein

complex (for example, using SEQ ID NO:601/UL9). In the presence of a stabilizing molecule, the half-life, as detected by the capture system time points, will be shortened.

Using the capture system for DNA:protein complexes to detect molecules that increase the affinity of the DNA-binding protein for the screening sequence requires that an excess of unlabeled oligonucleotide containing the UL9 binding site (but not the test sequences) is added to the assay mixture. This is, in effect, an off-rate experiment. In this case, the control sample (no test molecules or mixtures added) will show a fixed off-rate. For example, samples would be taken at fixed intervals after the addition of the unlabeled competition DNA molecule, applied to nitrocellulose, and a decreasing amount of radiolabeled DNA:protein complex would be observed). In the presence of a DNA-binding test molecule that enhanced the binding of UL9, the off-rate would be decreased (*i.e.*, the amount of radiolabeled DNA:protein complexes observed would not decrease as rapidly at the fixed time points as in the control sample).

VI. Utility.

A. The Usefulness of Sequence-Specific DNA-Binding Molecules.

The present invention defines a high through-put *in vitro* screening assay to test large libraries of biological or chemical mixtures for the presence of DNA-binding molecules having sequence binding preference. The assay is also capable of determining the sequence-specificity and relative affinity of known DNA-binding molecules or purified unknown DNA-binding molecules. Sequence-specific DNA-binding molecules are of particular interest for several reasons, which are

listed here. These reasons, in part, outline the rationale for determining the usefulness of DNA-binding molecules as therapeutic agents:

First, for a given DNA:protein interaction, there are generally several thousands fewer target DNA-binding sequences per cell than protein molecules that bind to the DNA. Accordingly, even fairly toxic molecules might be delivered in sufficiently low concentration to exert a biological effect by binding to the target DNA sequences.

Second, DNA has a relatively more well-defined structure compared to RNA or protein. Since the general structure of DNA has less tertiary structural variation, identifying or designing specific binding molecules should be easier for DNA than for either RNA or protein. Double-stranded DNA is a repeating structure of deoxyribonucleotides that stack atop one another to form a linear helical structure. In this manner, DNA has a regularly repeating "lattice" structure that makes it particularly amenable to molecular modeling refinements and hence, drug design and development.

Third, since many single genes (*i.e.*, genes which have only 1 or 2 copies in the cell) are transcribed into more than one, potentially as many as thousands of RNA molecules, each of which may be translated into many proteins, targeting <u>any</u> DNA site, whether it is a regulatory sequence, non-coding sequence or a coding sequence, may require a much lower drug dose than targeting RNAs or proteins. Proteins (*e.g.*, enzymes, receptors, or structural proteins) are currently the targets of most therapeutic agents. More recently, RNA molecules have become the targets for antisense or ribozyme therapeutic molecules.

Fourth, blocking the function of a RNA that encodes a protein or of the protein itself when that protein regulates several cellular genes may have detrimental effects: particularly if some of the regulated genes are important for the survival of the cell. However, blocking a DNA-binding site that is specific to a single gene regulated by such a protein results in reduced toxicity.

An example situation is HNF-1 binding to Hepatitis B virus (HBV): HNF-1 binds an HBV enhancer sequence and stimulates transcription of HBV genes (Chang, *et al.*). In a normal cell HNF-1 is a nuclear protein that appears to be important for the regulation of many genes, particularly liver-specific genes (Courtois, *et al.*). If molecules were isolated that specifically bound to the DNA-binding domain of HNF-1, all of the genes regulated by HNF-1 would be down-regulated, including both viral and cellular genes. Such a drug could be lethal since many of the genes regulated by HNF-1 may be necessary for liver function. However, the assay of the present invention presents the ability to screen for a molecule that could distinguish the HNF-1 binding region of the Hepatitis B virus DNA from cellular HNF-1 sites by, for example, including divergent flanking sequences when screening for the molecule. Such a molecule would specifically block HBV expression without effecting cellular gene expression.

B. <u>General Applications of the Assay</u>.

General applications of the assay include but are not limited to: screening libraries of unknown chemicals, either biological or synthetic compounds, for sequence-specific DNA-binding molecules, determining the sequence-specificity or preference and/or relative affinities of DNA-binding molecules, testing

of modified derivatives of DNA-binding molecules for altered specificity or affinity, using the assay in secondary confirmatory or mechanistic experiments, using the data generated from the above applications to refine the predictive capabilities of molecular modeling systems, and using the refined molecular modeling systems to generate a new "alphabet" of DNA-binding subunits that can be polymerized to make novel heteropolymers designed *de novo* to bind specific DNA target sites.

1. Mass-Screening of Libraries for the Presence of Sequence-Specific DNA-Binding Molecules.

Many organizations (*e.g.*, the National Institutes of Health, pharmaceutical and chemical corporations) have large libraries of chemical or biological compounds from synthetic processes or fermentation broths or extracts that may contain as yet unidentified DNA-binding molecules. One utility of the assay is to apply the assay system to the mass-screening of these libraries of different broths, extracts, or mixtures to detect the specific samples that contain the DNA-binding molecules. Once the specific mixtures that contain the DNA-binding molecules have been identified, the assay has a further usefulness in aiding in the purification of the DNA-binding molecule from the crude mixture. As purification schemes are applied to the mixture, the assay can be used to test the fractions for DNA-binding activity. The assay is amenable to high throughput (*e.g.*, a 96-well plate format automated on robotics equipment such as a Beckman Biomek workstation [Beckman, Palo Alto, CA] with detection using semi-automated plate-reading densitometers, luminometers, or phosphoimagers).

The concentration of protein used in mass-screening is determined by the sensitivity desired. The screening of known compounds, as described in Section VI.B.2, is typically performed in protein excess at a protein concentration high enough to produce 90-95% of the DNA bound in DNA:protein complex. The assay is very sensitive to discriminatory inhibition at this protein concentration. For some mass-screening, it may be desirable to operate the assay under higher protein concentration, thus decreasing the sensitivity of the assay so that only fairly high affinity molecules will be detected: for example, when screening fermentation broths with the intent of identifying high affinity binding molecules. The range of sensitivities in the assay will be determined by the absolute concentration of protein used.

One utility of the method of the present invention, under conditions using a relatively insensitive system (high [P]:[D] ratio), is as a screening system for novel restriction enzymes. In this case, an ability to discriminate between slight differences in affinity to different sequences may not be necessary or desirable. Restriction enzymes have highly discriminatory recognition properties -- the affinity constant of a restriction endonuclease for its specific recognition sequence versus non-specific sequences are orders of magnitude different from one another. The assay may be used to screen bacterial extracts for the presence of novel restriction endonucleases. The 256 test oligonucleotides described in Example 10, for example, may be used to screen for novel restriction endonucleases with 4 bp recognition sequences. The advantages of the system are that all possible 4 bp sequences are screened simultaneously, that is, it is not limited to self-complementary sequences. Further, any lack of

specificity (such as, more than one binding site) is uncovered during the primary screening assay.

2. Directed Screening.

The assay of the present invention is also useful for screening molecules that are currently described in the literature as DNA-binding molecules but with uncertain DNA-binding sequence specificity (*i.e.*, having either no well-defined preference for binding to specific DNA sequences or having certain higher affinity binding sites but without defining the relative preference for all possible DNA binding sequences). The assay can be used to determine the specific binding sites for DNA-binding molecules, among all possible choices of sequence that bind with high, low, or moderate affinity to the DNA-binding molecule. Actinomycin D, Distamycin A, and Doxorubicin (Example 6) all provide examples of molecules with these modes of binding. Many anti-cancer drugs, such as Doxorubicin (see Example 6), show binding preference for certain identified DNA sequences, although the absolute highest and lowest specificity sequences have yet to be determined, because, until the invention described herein, methods (Salas and Portugal; Cullinane and Phillips; Phillips; and Phillips, *et al.*) for detecting differential affinity DNA-binding sites for any drug were limited. Doxorubicin is one of the most widely used anti-cancer drugs currently available. As shown in Example 6, Doxorubicin is known to bind some sequences preferentially. Another example of such sequence binding preference is Daunorubicin (Chen, *et al.*) which differs slightly in structure from Doxorubicin (Goodman, *et al.*). Both Daunorubicin and Doxorubicin are members of the anthracycline antibiotic family: antibiotics in this family, and their deriva-

tives, are among the most important newer antitumor agents (Goodman, *et al.*).

The assay of the present invention allows the sequence preferences or specificities of DNA-binding molecules to be determined. The DNA-binding molecules for which sequence preference or specificity can be determined may include small molecules such as aminoacridines and polycyclic hydrocarbons, planar dyes, various DNA-binding antibiotics and anticancer drugs, as well as DNA-binding macromolecules, such as, peptides and polymers that bind to nucleic acids (*e.g.*, DNA and the derivatized homologs of DNA that bind to the DNA helix).

The molecules that can be tested in the assay for sequence preference/specificity and relative affinity to different DNA sites include both major and minor groove binding molecules as well as intercalating and non-intercalating DNA binding molecules.

3. Molecules Derived from Known DNA-binding Molecules.

The assay of the present invention facilitates the identification of different binding activities by molecules derived from known DNA-binding molecules. An example of this would be to identify and test derivatives of anti-cancer drugs that have DNA-binding activity and then test for anti-cancer activity through, for example, a battery of assays performed by the National Cancer Institute (Bethesda MD). Further, the assay of the present invention can be used to test derivatives of known anti-cancer agents to examine the effect of the modifications on DNA-binding activity and specificity. In this manner, the assay may reveal activities of anti-cancer agents, and derivatives of these agents, that facilitate the design of DNA-binding

molecules with therapeutic or diagnostic applications in different fields, such as antiviral or antimicrobial therapeutics. The binding-activity information for any DNA-binding molecule, obtained by application of the present assay, can lead to a better understanding of the mode of action of more effective therapeutics.

4. Secondary Assays.

As described above, the assay of the present invention is used (i) as a screening assay to detect novel DNA-binding molecules, or (ii) to determine the relative specificity and affinity of known molecules (or their derivatives). The assay may also be used in confirmatory studies or studies to elucidate the binding characteristics of DNA-binding molecules. Using the assay as a tool for secondary studies can be of significant importance to the design of novel DNA-binding molecules with altered or enhanced binding specificities and affinities.

a.) Confirmatory Studies.

The assay of the present invention can be used in competition studies to confirm and refine the original direct binding data obtained from the assay.

The primary screening assay does not provide for the direct determination of relative absolute affinities of test molecules for different test sequences. A competition method has been developed that aids in the interpretation and confirmation of the primary screening assay. The competition method also provides a means for determining the minimum difference in absolute affinities of any test sequences for a given test molecule.

Sequences of interest are tested for their ability to compete with the test oligonucleotide for binding a

test molecule of interest. In this method, DNA molecules that contain sequences that are high affinity binding sites for the DNA-binding test molecule compete effectively with the test oligonucleotide for the binding of the test molecule. DNA molecules that contain sequences that are low affinity binding sites for the test molecules are ineffective competitors. In effect, the fold-difference in concentration required between a high affinity competitor DNA and a low affinity competitor DNA, where the competitor is required to compete with the test oligonucleotide for the binding of the DNA-binding test molecule, should be proportional to the difference in affinity between the two competitor DNA molecules.

Any test oligonucleotide may be used in the competition study. However, in practice, since most secondary screening will be used to examine the putative high affinity binding test sequences, the secondary competition assay is typically used to test a competitor oligonucleotide which is a putative high affinity test sequence.

In the competition assay, the assay conditions are essentially the same as the conditions used in the primary screening assay. The assay components are mixed, with the exception of the DNA. The mixture includes protein, buffer and the DNA-binding test molecule (control samples lack the test molecule). A test oligonucleotide is labeled (for example, using a radioisotope, although any of the described capture/detection systems should be effective in the competition study). The DNA sample, including the radiolabeled test oligonucleotide and unlabelled competitor DNA is added to the assay mixture. Typically, the competitor DNA of interest is added to different reactions over a range of competitor concentrations. Two controls are

commonly run: (i) no DNA binding test molecule added; and (ii) test DNA but no competitor DNA added.

The reactions are incubated for the desired time and the DNA:protein complexes separated from free DNA (*i.e.*, DNA not associated with protein) by passing the mixture through nitrocellulose. Other capture systems, such as the biotin/streptavidin system discussed in Section V, are also effective. The amount of radiolabeled test oligonucleotide bound by protein (*i.e.*, bound to the filter) is indicative of the effect of the competitor.

One example of a competition assay is as follows. A test oligonucleotide containing the test sequence TTAC ranks as a high affinity binding site for a test molecule. The TTAC test oligonucleotide is radiolabeled and mixed with non-radiolabeled competitor DNAs that contain, for example, a putative high affinity binding site (the same site, TTAC, is one example) or a putative low affinity binding site (*e.g.*, CCCC). In the absence of any competing nonlabeled DNA or DNA-binding test molecule, the amount of radiolabeled DNA:protein complex observed (called r%) is arbitrarily established as 100%. The concentration of the protein used in this experiment is high enough to bind most of the radiolabelled test oligonucleotide in the absence of test molecules or competing DNA molecules (this is essentially the same concentration as used in the primary screening assay).

The test molecule is added to the reaction at a concentration sufficient to markedly reduce r%, the amount of observed DNA:protein complex. The greater the reduction in signal, the more easily competition is observed. The amount of competitor DNA needed to observe competition is proportional to the amount of DNA-binding test molecule used; therefore, the amount

of test molecule used should be sufficient to reduce r% to between approximately 10% to 70%. The effect of an effective competitor, such as TTAC, is to cause r% to rise towards 100%.

The competition for test molecule binding is between the non-labeled competitor DNA and the radiolabeled test oligonucleotide. As the competitor DNA concentration increases, the test molectule binds to the competitor DNA and is effectively removed from solution. Accordingly, the test molecule is no longer able to block the binding of the protein to the radiolabeled oligonucleotide. A less effective competitor, typically a competitor DNA with low affinity for the test molecule, will compete less effectively for the DNA-binding test molecule, even at substantially higher concentrations than the high affinity competitor. A completely ineffective competitor, *i.e.*, one that did not bind the test molecule, would not cause the r% value to change, even at high concentrations of the competitor DNA.

When a competitor DNA has some affinity for the test molecule, competition (r% rising towards 100%) would be observed at some competitor DNA concentration. The difference in concentration between two competing DNA sequences to achieve an equivalent r% (*e.g.*, 90%) should reflect the relative difference in absolute affinity between the two competitor DNA molecules. For example, if 5 μM TTAC is required to achieve a change in r% from 50% to 90% in the presence of a test molecule and 200 μM CCCC is required to achieve the same change in r%, then the fold difference in affinity between TTAC and CCCC for the test molecule is 200/5 = 40-fold.

In the context of screening distamycin with all possible 256 bp test sequences (Example 10), the

confirmatory assay can be used (i) to confirm the rankings observed in the assay, (ii) to refine the rankings among the 5-10 highest ranked binders (which show no statistical difference in rank with data from 4 experiments), and (iii) to resolve perceived discrepancies in the assay data. All of these goals may be accomplished using a competition experiment which determines the relative ability of test sequences to compete for the binding of distamycin.

The perceived discrepancy in the distamycin experiment is as follows: test oligonucleotides scored poorly in the assay which were complementary to most of the top-ranking test sequence oligonucleotides (Examples 10 and 11). This result was unexpected since it is unlikely that the affinity of distamycin for binding a test site depends on the orientation of the screening site to the test site. More likely, the assay detects the binding of distamycin when the molecule is bound to the test oligonucleotide in one orientation, but fails to detect the binding of distamycin when the test sequence is in the other orientation. A competition study will resolve this question, since the binding of distamycin to a competitor sequence will be orientation-independent; the competition does not depend on the mechanism of the assay.

For the competition experiment, the assay may be performed under any conditions suitable for the detection of drug binding. When these conditions are established, different competitor DNAs are added to the assay system to determine their relative ability to compete for drug binding with the radiolabeled test oligonucleotide in the assay system.

The competitor DNAs may be any sequence of interest. Several classes of DNA may be tested as competitor molecules including, but not limited to, the

following: genomic DNAs, synthetic DNAs (*e.g.*, poly(dA), poly(dI-dC), and other DNA polymers), test oligonucleotides of varying sequences, or any molecule of interest that is thought to compete for distamycin binding.

When using the competition assay to verify the results of a 256 oligonucleotide panel screen (like Example 10), the following criteria are useful for selecting the competitor test oligonucleotides:

(i) sequences that rank high in the assay but which do not have relative binding affinities with differences that are statistically significant from each other, in order to determine their relative affinity with greater precision;

(ii) sequences that are purported by other techniques (*e.g.*, footprinting or transcriptional block analysis) to be high affinity binding sites, in order to compare the results of those techniques with the screening assay results;

(iii) sequences that are complementary to test sequences that rank high in the assay, in order to determine whether these test sequences are false negatives; and

(iv) sequences of any rank in the assay, in order to confirm the assay results.

Several methods may be used to perform the competition study as long as the relative affinities of the competing DNA molecules are detectable. One such method is described in Example 14. In this example, the concentration of the assay components (drug, protein, and DNA) is held constant relative to those used in the original screening assay, but the molar ratio of the test oligonucleotide to the competitor oligonucleotides is varied.

Another method for performing a competition assay is to hold the concentrations of protein, drug and initial amount of test oligonucleotide constant, then add a variable concentration of competitor DNA. In this design, the protein and drug concentration must be sufficiently high to allow the addition of further competitor DNA without i) decreasing the amount of DNA:protein complex in the absence of drug to a level that is unsuitable for detection of DNA:protein complex, and ii) increasing the amount of DNA:protein complex in the presence of drug to a level that is unsuitable for the detection of drug binding. The window between detectable DNA:protein complex and detectable effect of the drug must be wide enough to determine differences among competitor DNAs.

In any competition method, it is important that the relative concentrations of the competing DNA molecules are accurately determined. One method for accomplishing accurate determination of the relative concentrations of the DNA molecules is to tracer-label competitor molecules to a low specific activity with a common radiolabeled primer (Example 14). In this manner, the competitor molecules have the same specific activity, but are not sufficiently radioactive (200-fold less than the test oligonucleotide) to contribute to the overall radioactivity in the assay.

b.) <u>Secondary Studies to Elucidate Binding Characteristics</u>. The studies outlined in Section VI.B.4.a describe methods of determining some of the binding processes of distamycin A. The assay of the present invention may also be used to explore mechanistic questions about distamycin binding.

For example, several of the complements of the putative high affinity binding sites for distamycin

have low scores in the assay. As described above, this may imply directionality in binding. The results may also imply that the test sites are not equal with respect to the effect exerted on UL9-COOH binding. Oligonucleotides can be designed to test the hypothesis of directionality.

The basic test oligonucleotide has the structure presented in Figure 27A (SEQ ID NO:621). In one scenario, the score in the binding assay is high, *i.e.*, the greatest effect of distamycin, when the test sequences is XYZZ (Figure 27A, with the base X complementary to the base Y and the base Q complementary to the base Z), and the complement (Figure 27B; SEQ ID NO:622) scores low. These results imply that the test sites are not equivalent with respect to their effect on UL9, otherwise the right side would have the effect in one oligonucleotide and the left site would have the effect in the other. These results further suggest that the effect of distamycin is directional. The only assumption is that distamycin should bind with the same affinity to the XYZZ/QQXY sequence (Figures 27A and 27B) regardless of its position or orientation in the oligonucleotide. Since the scores are derived at equilibrium, this is likely to be the case.

To test the hypothesis that one site is effective in the assay, oligonucleotides may be designed that have the UL9 site inverted with respect to the test sites (Figures 27C and 27D; SEQ ID NO:623 and SEQ ID NO:624, respectively). If only one site is active with respect to UL9 and if the Figure 27A oligo was most effective in binding distamycin, then the oligo C should be less active in the assay then oligo D; in other words, flipping the UL9 site will result in QQXY ranking high, XYZZ ranking low.

Finally, to determine the "direction" of distamycin binding, mix test sequences and invert the binding site as shown in the four oligonucleotides presented in Figures 27E, 27F, 27G and 27H. Alternatively, one test site or the other could be deleted from the test oligonucleotide.

This type of analysis provides an example of the usefulness in the assay in determining binding properties of DNA-binding drugs.

c.) Restriction Endonucleases as Indicator Proteins in the Assay. Other DNA:protein interactions that are useful as screening sequences and their cognate binding proteins (indicator proteins) are restriction enzymes. Such secondary screening assays are performed using the same criteria to establish conditions for the primary screening assay (described in Example 4). The assay conditions can be varied to accommodate different DNA:protein interactions, as long as the assay system follows the functional criteria discussed above (Section I).

One limitation of using restriction endonucleases in the method of the present invention is that the assay buffer should not contain divalent cations. In the absence of divalent cations, the enzymes will bind the appropriate recognition sequence, but not cleave the DNA. In the presence of divalent cations, the test oligonucleotide can be cleaved at or near the protein binding site.

By using different indicator proteins, a different recognition sequence can be used to flank the test site. This variation allows the resolution of questions regarding the potential binding of a test molecule to a site internal to any single screening sequence. For example, the assay system is used where

the UL9 protein and its recognition sequence are used as the indicator protein:screening sequence interaction. In this system, if the highest affinity binding site for a test molecule is TTAC, then several test sequences may be predicted to rank high in the assay system: several of these test sequences are presented in Figure 31. In Figure 31, the test site is shown in bold, the potential binding site for the test molecule is shown underlined.

One test oligonucleotide on which the DNA-binding test molecule would be predicted to have a high level of effect is the oligonucleotide containing the test site, TTAC (Figure 31). However, since the UL9 recognition sequence contains the sequence TT, flanking the test site, several other test oligonucleotides might also be expected to have high activity in the assay (see Figure 31).

By using a different DNA:protein interaction as the indicator system in a secondary screening assay, the "false positives" shown for TACN and ACNN (shown in Figure 31) can be identified. The recognition sequence for the protein in a secondary screening assay simply needs to have a different screening sequence in the region flanking the test site than the UL9 screening sequence.

Restriction endonucleases provide an entire class of different DNA:protein interactions with a wide array of available sequences that can be used in this manner. For example, *SmaI* recognizes the sequence 5'-CCCGGG-3'. Using the *SmaI*:DNA interaction and the same test sequences presented in Figure 31, the resulting test oligonucleotides would have the test sequences presented in Figure 32. As can be seen from a comparison of Figures 31 and 32, changing the screening sequence from the UL9-binding sequence to the *SmaI*-binding sequence

eliminates the potential test molecule binding sites internal to the screening sequence (*e.g.*, compare TACN and ACNN in the figures).

The use of different DNA-binding proteins as indicator proteins in the assay is also applicable to the PCR-based test oligonucleotide selection technology (Section III).

5. <u>Generation of Binding Data and Refinement of Molecular Modeling Systems</u>.

The assay of the present invention generates data which can be applied to the refinement of molecular modeling systems that address DNA structural analysis: the data is also useful in the design and/or refinement of DNA-binding drugs. Traditionally, mass screening has been the only reasonable method for discovering new drugs. Modern rational drug design seeks to minimize laboratory screening. However, *ab initio* rational drug design is difficult at this time given (i) insufficiencies in the underlying theories used for *de novo* design, and (ii) the computational intensity which accompanies such design approaches.

The *ab initio* approach requires calculations from first principles by quantum mechanics: such an approach is expensive and time-consuming. The introduction of data concerning the relative binding affinities of one or more DNA-binding molecules to all 256 four base pair DNA sequences allows the development, via molecular modeling, of *ad hoc* protocols for DNA structural analysis and subsequent DNA-binding drug design. The accumulation of data for the DNA sequences to which small molecules bind is likely to result in more accurate, less expensive molecular modeling programs for the analysis of DNA.

The screening capacity of the assay of the present invention is much greater than screening a single DNA sequence with an individual cognate DNA-binding protein. Direct competition assays involving individual receptor:ligand complexes (*e.g.*, a specific DNA:protein complex) are most commonly used for mass screening efforts. Each such assay requires the identification, isolation, purification, and production of the assay components. In particular, a suitable DNA:protein interactions must be identified for each selected screening sequence. Using the assay of the present invention, libraries of synthetic chemicals or biological molecules can be screened to detect molecules that have preferential binding to virtually any specified DNA sequence -- all using a single assay system. When employing the assay of the present invention, secondary screens involving the specific DNA:protein interaction may not be necessary, since inhibitory molecules detected in the assay may be tested directly on a biological system: for example, the ability to disrupt viral replication in a tissue culture or animal model.

6. The Design of New DNA-Binding Heteropolymers Comprised of Subunits Directed to Different DNA Sequences.

The assay of the present invention will facilitate the predictive abilities of molecular modeling systems in two ways. First, *ad hoc* methods of structural prediction will be improved. Second, by employing pattern matching schemes, the comparison of sequences having similar or different affinities for a given set of DNA-binding molecules should empirically reveal sets of sequences that have similar structures (see Section VI.D, Using a Test Matrix). Molecular modeling programs are "trained" using the information

concerning DNA-binding molecules and their preferred binding sequences. With this information coupled to the predicative power of molecular modeling programs, the design of DNA-binding molecules (subunits) that could be covalently linked becomes feasible.

These molecular subunits would be directed at defined sections of DNA. For example, a subunit would be designed for each possible DNA unit. For example, if single bases were the binding target of the subunits, then four subunits would be required, one to correspond to each base pair. These subunits could then be linked together to form a DNA-binding polymer, where the DNA binding preference of the polymer corresponds to the sequence binding preferences of the subunits in the particular order in which the subunits are assembled.

Another example of such a polymer is using subunits whose binding was directed at two base sections of DNA. In this case, $4^2 = 16$ subunits would be used, each subunit having a binding affinity for a specific two base pair sequence (*e.g.*, AA, AC, AG, AT, CA, CC, CG, CT, GA, GC, GG, GT, TA, TC, TG, TT). If the polymers were to be comprised of subunits targeted to 3 base pair sections of DNA, then $4^3 = 64$ subunits would be prepared. The design of such molecular subunits is dependent upon the establishment of a refined database using empirical data derived by the method of the present invention, as described in Section VI.B.

C. <u>Sequences Targeted by the Assay</u>.

The DNA:protein assay of the present invention has been designed to screen for compounds that bind a full range of DNA sequences that vary in length as well as complexity. Sequence-specific DNA-binding molecules

discovered by the assay have potential usefulness as either molecular reagents, therapeutics, or therapeutic precursors. Sequence-specific DNA-binding molecules are potentially powerful therapeutics for essentially any disease or condition that in some way involves DNA. Examples of test sequences for the assay include: a) binding sequences of factors involved in the maintenance or propagation of infectious agents, especially viruses, bacteria, yeast and other fungi, b) sequences causing the inappropriate expression of certain cellular genes, and c) sequences involved in the replication of rapidly growing cells. Furthermore, gene expression or replication need not necessarily be disrupted by blocking the binding of specific proteins. Specific sequences within protein-coding regions of genes (*e.g.*, oncogenes) are equally valid test sequences since the binding of small molecules to these sequences is likely to perturb the transcription and/or replication of the region. Finally, any molecules that bind DNA with some sequence specificity, that is, not just to one particular test sequence, may be still be useful as anti-cancer agents. Several small molecules with some sequence preference are already in use as anticancer therapeutics. Molecules identified by the present assay may be particularly valuable as lead compounds for the development of congeners having either different specificity or different affinity.

One advantage of the present invention is that the assay is capable of screening for binding activity directed against any DNA sequence. Such sequences can be medically significant target sequences scrambled or randomly generated DNA sequences, or well-defined, ordered sets of DNA sequences. Other sets could be used for screening for molecules demonstrating sequence preferential binding (like Doxorubicin) to determine

the sequences with highest binding affinity and/or to determine the relative affinities between a large number of different sequences. There is usefulness in taking either approach for detecting and/or designing new therapeutic agents. Section VI.C.3, "Theoretical Considerations for Choosing Target Sequences", outlines the theoretical considerations for choosing DNA target sites in a biological system.

1. Medically Significant Target Sequences.

Few effective viral therapeutics are currently available; yet several potential target sequences for antiviral DNA-binding drugs have been well-characterized. Furthermore, with the accumulation of sequence data on all biological systems, including viral genomes, cellular genomes, pathogen genomes (bacteria, fungi, eukaryotic parasites, etc.), the number of target sites for DNA-binding drugs will increase greatly in the future.

There are numerous methods for identifying medically significant target sequences for DNA-binding drugs, including, but not limited to, the following. First, medically significant target sequences are found in pathogens of the biological kingdoms, for example in genetic sequences that are key to biochemical pathways or physiological processes. Second, a target is identified, such as (i) a pathogen involved in an infectious disease, or (ii) a biochemical pathway or physiological process of a noninfectious disease, genetic condition, or other biological process. Then specific genes important for the survival of the pathogen or modulation of the endogenous pathway involved in the target system are identified. Third, specific target sequences are identified that affect

the expression or activity of a DNA molecule, such as genes or sites involved in replication.

There are numerous pathogens that are potential targets for DNA-binding drugs designed using the methods described in this application. Table I lists a number of potential target pathogens.

Table I: Pathogens
VIRUSES
Retroviruses
Human
HIV I ,II
HTLV I, II
Animal
SIV
STLV I
FELV
FIV
BLV
BIV (Bovine immunodeficiency virus)
Lentiviruses
Avian reticuloendotheliosis virus
Animal - *continued*
SIV
STLV I
FELV
FIV
BLV
BIV (Bovine immunodeficiency virus)
Lentiviruses
Avian reticuloendotheliosis virus
Avian sarcoma and leukosis viruses
Caprine arthritis-encephalitis
Equine infectious anemia virus
Maedi/visna of sheep
MMTV (mouse mammary tumor virus)
Progressive pneumonia virus of sheep
Herpesviridae
Human
EBV
CMV

- HSV I, II
- VZV
- HH6
- Cercopthecine Herpes Virus (B Virus)
  - Old world monkeys with infection into humans.

Animal

- Bovine Mammillitis virus
- Equine Herpes virus
- Equine coital exanthema virus
- Equine rhinopneumonitis virus
- Infectious bovine rhinotracheitis virus
- Marek's disease virus of fowl
- Turkey herpesvirus

Hepadnaviruses

Human

- HBV/HDV

Animal

- Duck Hepatitis
- Woodchucks
- Squirrels

Poxviridae

Human

- Orf virus
- Cow Pox
- Variola virus
- Vaccinia
- Small Pox
- Pseudocowpox

Poxviridae - *continued*

Animal

- Bovine papular stomatitis virus
- Cowpox virus
- Ectromelia virus (mouse pox)
- Fibroma viruses of rabbits/squirrels
- Fowlpox
- Lumpy skin disease of cattle virus
- Myxoma
- Pseudocowpox virus
- Sheep pox virus
- Swine pox

Papovaviridae Human BK virus SV-40 JC virus Human Papillomaviruses 1-58 (see list Fields) Animal Lymphotropic papovavirus (LPV) Monkey Bovine papillomavirus Shope papillomavirus
Adenoviridae Human Adenoviruses 1-4 Animal Canine adenoviruses 2
Parvoviridae Human AAV (Adeno Associated Virus) B19 (human)
Animal FPV (Feline parvovirus) PPV (Porcine parvovirus) ADV (Aleutian disease, mink) Bovine Parvovirus Canine Parvovirus Feline panleukopenia virus Minute virus of mice Mink enteritis virus
BACTERIA
Streptococcus *pneumonia* bovis
Group A Streptococci Agents responsible for: Streptococcal pharyngitis Cervical adenitis Otitis media Mastoiditis Peritonsillar abscesses Meningitis Peritonitis

Pneumonia Acute glomerulonephritis Rheumatic fever Erythema nodosum
Staphylococcus aureus epidermidis saprophyticus *cohnii* *haemolytilcus* *xylosus* *warneri*
capitis hominis silmulans saccharolyticus auricularis Agents responsible for: Furunckles Carbuncles Osteomyelitis Deep tissue abscesses Wound infections Pneumonia Empyema Pericarditis Endocarditis Meningitis Purulent arthritis Enterotoxin in food poisoning
Branhamella catarrhalis
Neisseria *gonorrhoea* *lactamica* *sicca* *subflava* *mucosa*
Neisseria - continued flavescens cinerea elongata canis *meningitides*

Enteric Bacilli and Similar Gram-Negative Bacteria *Escherichia* *Proteus* *Klebsiella* *Pseudomonas aeruginosa* *Enterobacter* *Citrobacter* *Proteus*
Providencia *Bacteroides* *Serratia* *Pseudomonas* (not aeruginosa) *Acinetobacter* *Salmonella* *Shigella* *Aeromonas* *Moraxella* *Edwardsiella* *Ewingella* *Hafnia* *Kluyvera* *Morganella* *Plesiomonas*
Pseudomonas *aeruginosa* *putida* *pseudomallei* *mallei*
Haemophilus *ducreyi* *influenzae* *parainfluenzae*
Bordetella pertussis
Yersinia *pestis* (plague) *pseudotuberculosis* *enterocolitica*
Francisella tularensis
Pasteurella multocida
Vibrio *cholerae* *parhaemolyticus*

fluvialis *furnissii* *mimicus*
Brucella *melitensis* *abortus* *suis* *canis*
Bartonella bacilliformis
Gardnerella vaginalis
Borrelia *recurrentis* *hermsii* *duttoni* *crocidurae* *burgdorferi* (Lyme disease)
Bacillus *anthracis* *cereus* *megaterium* *subtilis* *sphaericus* *circulans* *brevis* *lentiformis* *macerans* *pumilus* *thuringiensis* *larvae* *lentimorbus* *popilliae*
Streptobacillus moniliformis (rat bite fever)
Spirillum minus (rat bite fever)
Rothia dentocariosa
Kurthia
Clostridium *botulinum* *nouyi* *bifermentans*

Clostridium - continued histolyticum ramosum tetani perfringens novyi septicum
Campylobacter *jejuni* *fetus* *hyintestinalis* *fennelliae* *cinaedi*
Corynebacterium *ulcerans* *pseudotuberculosis* *JK* *diphtheriae*
Legionella *pneumophila* *bosemanii* *micdadie* *bosenamii* *feleii* many others
Mycobacterium *tuberculosis* *africanum* *bovis* *leprae* *avium complex* *kansasii* *fortuitum complex* *scrofulaceum* *marinum* *ulcerans*
Actinomyces
Bacteroides *fragiligis*
Fusobacterium *necrophorum* *nucleatum*
Peptostreptococcus
Arachnia

Bifidobacterium
Propionibacterium
Nocardia
Treponema pallidum (syphilis)
Rickettsiae Typhus *R. prowazeki* (epidemic) *R. prowazeki* (Brill's disease) *R. typhi* (endemic) Spotted fever *R. rickettsi* *R. sibiricus* *R. conorii* *R. australis* *R. akari* Scrub typhus *R. tsutsugamushi* Q fever *Coxiella burnetii* Trench fever *Rochalimaea quintana*
Chlamydiae *C. trachomatis* (blindness, pelvic inflammatory disease, LGV)
Mycoplasma *pneumoniae* *Ureaplasma urealyticum*
Cardiobacterium hominis
Actinobacillus actinomycetemcomitans
Kingella
Capnocytophaga
Pasteurella multocida
Leptospira interrogans
Listeria monocytogenes
Erysipelothrix rhusiopthiae
Streptobacillus moniliformis
Calymmatobacterium granulomatis
Bartonella bacilliformis

Francisella tularensis
Salmonella typhi
FUNGAL
Actinomyces *israelii* *naeslundii* *viscosus* *odontolyticus* *meyeri* *pyogenes*
Cryptococcus neoformans
Blastomyces dermatitidis
Histoplasma capsulatum
Coccidioides immitis
Paracoccidioides brasiliensis
Candida *albicans* *tropicalis* *(Torulopsis) glabrata* *parapsilosis*
Aspergillus *fumigatus* *flavus* *niger* *terreus*
Rhinosporidiosis seeberi
Phycomycetes
Sporothrix schenickii
Mucorales
Entomophthorales
Agents of *Chromoblastomycosis*
Microsporum *M. audouilni* (ring worm) *M. canis* *M. gypseum*

Trichophyton *T. schoenleinii* (favus-ringworm) *T. violaceum* (hair) *T. tonsurans* (hair) *T. mentagrophytes* (athlete's foot) *T. rubrum* (athlete's foot)
Malassezia furfur
Cladosporium *werneckii* *carrioni*
Fonsecaea *pedrosoi* *compacta*
Phialophora verrucosa
Rhinocladiella aquaspersa
Trichosporon cutaneum
Piedraia hortai
Ascomycota
Basidiomycota
Deuteromycota
Norcardia *brasiliensis* *caviae* *asteroides*
PARASITIC PATHOGENS
Plasmodium (malaria) *falcilparum* *vivax* *ovale* *malariae*
Schistosoma *japonmicum* *mansoni* *haematobium* *intercalatum* *mekongi*

Trypanosoma
    brucei gambiense
    brucei rhodesiense
    evansi
    cruzi
    equiperdum
    congolense

Entamoeba histolytica
Naegleria fowleri

Acanthoamoeba
    astronyxis
    castellanii
    culbertsoni
    hatchetti
    palestinensis
    polyphaga
    rhyusodes

Leishmania
    dovonani
    infantum
    chagasi
    topica
    major
    aethiopica
    mexicana
    braziliensis
    peruviana

Pneumocystis carinii (interstitial pneumonia)

Babesia (tick born hemoprotozoan)
    microti
    divergens

Giardia lamblia

Trichomonas (venereal disease)
    vaginalis
    hominis
    tenax

Cryptosporidium parvum (intestinal protozoan)
Isopora belli (dysentery)
Balantidium coli (protozoon induced dysentery)
Dientamoeba fragilis
Blastocystis hominis

Trichinella spiralis (parasitic nematode)
Wuchereria bancrofti(lymphatic filariasis)
Brugia (lymphatic filariasis) *malayi* *timori*
Loa loa (eye worm)
Onchocerca volvulus
Mansonella *perstans* *ozzardi* *streptocerca*
Dirofilaria immitis
Angiostrongylus cantonensis *costaricensis* *malayensis* *mackerrasae*
Anisakis (nematode) *simplex* *typica*
Pseudoterranova decipiens
Gnathostoma spinigerum
Dracunculus medinensis (filarial parasite, guinea worm)
Trichuris trichiura (whip worm)
Ascaris lumbricoides (nematode)
Toxocara canis (nematode round worms)
Necator americanus (heart worm)
Ancylostoma (hook worm) *duodenale* *ceylanicum* *americanus*
members of the species *Trichostrongylus*
Strongyloides (intestinal nematode) *stercoralis* *fuelleborni*
Capillaria philippinensis (intestinal nematode)

Various species of *Paragonimus* (lung fluke disease)
Various species of *Micorsporida*
Clonorchis sinensis (liver fluke)
Fasciola (trematode, intestinal worm) *hepatica* *gigantica*
Fasciolopsis buski
Heterophyes heterophyes
Metagonimus yakagawa
Taenia *saginata* (beef tapeworm) *solium* (pork tapeworm)
Hymenolepis (dwarf tapeworm) *nana* *nana fraterna* *diminuta*
Dipylidium caninum (tapeworm of dogs and cats)
Diphyllobothrium (fish tapeworms) *lantum* *dalliae* *nihonkaiense* *pacificum*
Echinococcus (tape worm with cysts) *granulosus* *multilocularis* *vogeli*
Enterobius vermicularis (Pin worm)

In addition to pathogens, many non-infectious diseases may be controlled at the level of DNA. These diseases are therefore potential candidates for treatment with DNA-binding therapeutics that are discovered or designed using the methods described in this application. Table II lists a number of potential non-infectious diseases that may be targeted for treatment using DNA-binding molecules.

Table II: Noninfectious Diseases
CANCER
Lung Adenocarcinoma Squamous cell Small cell
Breast carcinoma
Ovarian Serous tumors Mucinous tumors Endometrioid carcinoma
Endometrial carcinoma
Colon carcinoma
Malignant Melanoma
Prostate carcinoma
Lymphoma Hodgkins Non-Hodgkin's
Leukemia Chronic Myelogenous Acute Myelogenous Chronic Lymphocytic Acute Lymphocytic
Cervical carcinoma
Seminoma
Multiple Myeloma
Bladder carcinoma
Pancreatic carcinoma
Stomach carcinoma
Thyroid Papillary adenocarcinoma Follicular carcinoma Medullary carcinoma
Oral & Pharyngeal carcinomas
Laryngeal carcinoma
Bladder carcinoma

Renal cell carcinoma
Hepatocellular carcinoma
Glioblastoma
Astrocytoma
Meningioma
Osteosarcoma
Pheochromocytoma
CARDIOVASCULAR DISEASES
Hypertension Essential Malignant
Acute Myocardial Infarction
Stroke Ischemic Hemorrhagic
Angina Pectoris
Unstable angina
Congestive Heart Failure
Supraventricular arrhythmias
Ventricular arrhythmias
Deep Venous Thrombosis
Pulmonary Embolism
Hypercholesterolemia
Cardiomyopathy
Hypertriglyceridemia
RESPIRATORY DISORDERS
Allergic rhinitis
Asthma
Emphysema
Chronic bronchitis
Cystic Fibrosis
Pneumoconiosis

Respiratory distress syndrome
Idiopathic pulmonary fibrosis
Primary pulmonary hypertension
GASTROINTESTINAL DISORDERS
Peptic ulcers
Cholelithiasis
Ulcerative colitis
Crohn's disease
Irritable Bowel Syndrome
Gastritis
Gilbert's syndrome
Nausea
ENDOCRINE/METABOLIC DISORDERS
Diabetes mellitus type I
Diabetes mellitus type II
Diabetes insipidus
Hypothyroidism
Hyperthyroidism
Gout
Wilson's disease
Addison's disease
Cushing's syndrome
Acromegaly
Dwarfism
Prolactinemia
Morbid obesity
Hyperparathyroidism
Hypoparathyroidism
Osteomalacia

RHEUMATOLOGY/IMMUNOLOGY DISORDERS
Transplant rejection
Systemic lupus erythematosus
Rheumatoid arthritis
Temporal Arteritis
Amyloidosis
Sarcoidosis
Sjogren's Syndrome
Scleroderma
Ankylosing spondylitis
Polymyositis
Reiter's Syndrome
Polyarteritis nodosa
Kawasaki's disease
HEMATOLOGIC DISORDERS
Anemia Sickle cell Siderablastic Hereditary spherocytosis Aplastic Autoimmune hemolytic anemia
Thalassemia
Disseminated intravascular coagulation
Polycythemia vera
Thrombocytopenia Thrombotic thrombocytopenic purpura Idiopathic thrombocytopenic purpura
Hemophilia
von Willebrand's disease
Neutropenia Post-chemotherapy Post-radiation

NEUROLOGIC DISORDERS
Alzheimer's disease
Parkinson's disease
Myasthenia gravis
Multiple sclerosis
Amyotrophic lateral sclerosis
Epilepsy
Headaches Migraine Cluster Tension
Guillain-Barre syndrome
Pain (post-op, trauma)
Vertigo
PSYCHIATRIC DISORDERS
Anxiety
Depression
Schizophrenia
Substance abuse
Manic-Depression
Anorexia
DERMATOLOGIC DISORDERS
Acne
Psoriasis
Eczema
Contact dermatitis
Pruritis
OPHTHALMIC DISORDERS
Glaucoma
Allergic conjunctivitis
Macular degeneration

MUSCULOSKELETAL DISORDERS
Osteoporosis
Muscular dystrophy
Osteoarthritis
GENETIC DISORDERS
Down's syndrome
Marfan's syndrome
Neurofibromatosis
Tay-Sachs disease
Gaucher's disease
Niemann-Pick disease
GENITAL-URINARY DISORDERS
Benign prostatic hypertrophy
Polycystic kidney disease
Non-infectious glomerulonephritis
Goodpasture's syndrome
Urolithiasis
Endometriosis
Impotence
Infertility
Fertility control
Menopause

Once a disease or condition is identified as a potential candidate for treatment with a DNA-binding therapeutic, specific genes or other DNA sequences that are crucial for the expression of the disease associated gene (or survival of a pathogen) are identified within the biochemical or physiological pathway (or the pathogen). In humans, many genes involved in important biological functions have been identified. Virtually

any DNA sequence is a potential target site for a DNA-binding molecule, including mRNA coding sequences, promoter sequences, origins of replication, and structural sequences, such as telomeres and centromeres. One class of sites that may be preferable are the recognition sequences for proteins that are involved in the regulation or expression of genetic material. For this reason, the promoter/regulatory regions of genes also provide potential target sites (Table III, see also Example 15).

Table III: Human Genes with Promoter Regions that are Potential Targets for DNA-Binding Molecules

*[LOCUS Names are from EMBL database ver. 33. 1992.]

LOCUS Names*	Locus Description
>HS5FDX	Human ferredoxin gene, 5' end.
>HSA1ATCA	Human macrophage alpha1-antitrypsin cap site region
>HSA1GPB1	Human gene B for alpha 1-acid glycoprotein exon 1 and 5'flank
>HSA1MBG1	Human gene for alpha-1-micro-globulin-bikunin, exons 1-5 (encoding
>HSA2MGLB1	H.sapiens gene for alpha-2 macroglobulin, exon 1
>HSACAA1	H.sapiens ACAA gene (exons 1 & 2) for peroxisomal 3-oxoacyl-CoA
>HSACCOA	Homo sapiens choline acetyltransferase gene sequence.
>HSACEB	Human angiotensin I-converting enzyme (ACE) gene, 5' flank.
>HSACHG1	Human gene fragment for the acetylcholine receptor gamma subunit
>HSACT2CK1	Human cytokine (Act-2) gene, exon 1.
>HSACTBPR	Human beta-actin gene 5'-flanking region

>HSACTCA	Human cardiac actin gene, 5′ flank.
>HSACTSA	Human gene for vascular smooth muscle alpha-actin (ACTSA), 5′
>HSACTSG1	Human enteric smooth muscle gamma-actin gene, exon 1.
>HSAD12L	Human arachidonate 12-lipoxygenase gene, 5′ end.
>HSADH1X	Human alcohol dehydrogenase alpha subunit (ADH1) gene, exon 1.
>HSADH2X	Human alcohol dehydrogenase beta subunit (ADH2) gene, exon 1.
>HSAFPCP	Human alpha-fetoprotein gene, complete cds.
>HSAK1	Human cytosolic adenylate kinase (AK1) gene, complete cds.
>HSAGAL	Human alpha-N- acetylgalactosaminidase (NAGA) gene, complete cds.
>HSALADG	H.sapiens ALAD gene for porphobilinogen synthase
>HSALBENH	Human albumin gene enhancer region.
>HSALDA1	Human aldolase A gene 5′ non-coding exons
>HSALDCG	Human aldolase C gene for fructose-1,6-bisphosphate aldolase
>HSALDOA	Human aldolase A gene (EC 4.1.2.13)
>HSALDOBG	Human DNA for aldolase B transcription start region
>HSALIFA	Human leukemia inhibitory factor (LIF) gene, complete cds.
>HSAMINON	Human aminopeptidase N gene, complete cds.
>HSAMY2A1	Human alpha-amylase (EC 3.2.1.1) gene AMY2A 5-flank and exon 1
>HSAMYB01	Human amyloid-beta protein (APP) gene, exon 1. 1154
>HSANFG1	Human gene fragment for pronatriodilatin precursor (exons 1 and 2)

>HSANFPRE	Human gene for atrial natriuretic factor (hANF) precursor
>HSANFZ1	Human atrial natriuretic factor gene, complete cds.
>HSANGG1	Human angiotensinogen gene 5'region and exon 1
>HSANT1	Human heart/skeletal muscle ATP/ADP translocator (ANT1) gene,
>HSAPC3A	Human apolipoprotein CIII gene and apo AI-apo CIII intergenic
>HSAPC3G	Human gene for apolipoprotein C-III
>HSAPOA2	Human gene for apolipoprotein AII
>HSAPOAIA	Human fetal gene for apolipoprotein AI precursor
>HSAPOBPRM	Human apoB gene 5' regulatory region (apolipoprotein B)
>HSAPOC2G	Human apoC-II gene for preproapo-lipoprotein C-II
>HSAPOCIA	Human apolipoprotein C-I (VLDL) gene, complete cds.
>HSAPOLIDG	H.sapiens promoter region of gene for apolipoprotein D
>HSARG1	Human arginase gene exon 1 and flanking regions (EC 3.5.3.1)
>HSASG5E	Human argininosuccinate synthetase gene 5' end 1105
>HSATP1A3S	Human sodium/potassium ATPase alpha 3 subunit (ATP1 A3) gene, 5'
>HSBSF2	Human (BSF-2/IL6) gene for B cell stimulatory factor-2
>HSC5GN	Human C5 gene, 5' end. 650
>HSCAII	Human gene fragment for carbonic anhydrase II (exons 1 and 2)
>HSCALCAC	Human calcitonin/alpha-CGRP gene
>HSCALRT1	Human DNA for calretinin exon 1
>HSCAPG	Human cathepsin G gene, complete cds.

>HSCAVII1	H.sapiens carbonic anhydrase VII (CA VII) gene, exon 1.
>HSCBMYHC	Human gene for cardiac beta myosin heavy chain
>HSCD3AA	Human complement C3 protein mRNA, 5' flank. >HSCD4 Human recognition/surface antigen (CD4) gene, 5' end.
>HSCD44A	Human hyaluronate receptor (CD44) gene, exon 1.
>HSCFTC	Human cystic fibrosis transmembrane conductance regulator gene, 5'
>HSCH7AHYR	Human cholesterol 7-alpha-hydroxylase (CYP7) gene, 5' end.
>HSCHAT	Human gene for choline acetyltransferase (EC 2.3.1.6), partial
>HSCHYMASE	Human mast cell chymase gene, complete cds.
>HSCHYMB	Human heart chymase gene, complete cds. 3279
>HSCKBG	Human gene for creatine kinase B (EC 2.7.3.2)
>HSCNP	Human C-type natriuretic peptide gene, complete cds.
>HSCD59011	Human transmembrane protein (CD59) gene, exon 1.
>HSCDPRO	Human myeloid specific CD11b promoter DNA.
>HSCETP1	Human cholesteryl ester transfer protein (CETP) gene, exons 1 and
>HSCFTC	Human cystic fibrosis transmembrane conductance regulator gene, 5'
>HSCOSEG	H.sapiens coseg gene for vasopressin-neurophysin precursor
>HSCREKIN	Human creatine kinase gene, exon 1.
>HSCRYABA	Human alpha-B-crystallin gene, 5' end.
>HSCS5P	Human C3 gene, 5' end.

>HSCSF1G1	Human gene for colony stimulating factor CSF-1 5' region
>HSCSPA	Human cytotoxic serine proteinase gene, complete cds.
>HSCST3G	Human CST3 gene for cystatin C
>HSCST4	H.sapiens CST4 gene for Cystatin D
>HSCYP2C8	Human CYP2C8 gene for cytochrome P-450, 5' flank and exon 1
>HSCYP45A	Human gene for cholesterol desmolase cytochrome P-450(SCC) exon 1
>HSCYPB1	Human steroid 11-beta-hydroxylase (CYP11B1) gene, exons 1 and 2.
>HSCYPXI	Human CYPXI gene for steroid 18-hydroxylase (P-450 C18). 2114
>HSCYPXIB1	Human CYPXIB gene for steroid 11beta-hydroxylase (P-450 11beta),
>HSCYPXIX	Human CYPXIX gene, exon 1 coding for aromatase P-450 (EC 1.14.14.1)
>HSDAFC1	Human decay-accelerating factor (DAF) gene, exons 1 and 2.
>HSDBH1	Human DNA for dopamine beta-hydroxylase exon 1 (EC 1.14.17.1)
>HSDES	Human desmin gene, complete cds.
>HSDKERB	Human cytokeratin 8 (CK8) gene, complete cds.
>HSDNAPOL	Human DNA polymerase alpha gene, 5' end.
>HSDOPAM	H.sapiens dopamine D1A receptor gene, complete exon 1, and exon 2,
>HSECP1	Human DNA for eosinophil cationic protein ECP
>HSEGFA1	Human HER2 gene, promoter region and exon 1.
>HSEL20	Human elastin gene, exon 1.
>HSELAM1B	Human endothelial leukocyte adhesion molecule I (ELAM-1) gene,

>HSEMBPA	Human eosinophil major basic protein gene, complete cds.
>HSENKB1	Human preproenkephalin B gene 5' region and exon 1
>HSENO35	Human ENO3 gene 5' end for muscle--specific enolase
>HSEOSDN	Human DNA for eosinophil derived neurotoxin
>HSEPR	Human erythropoietin receptor mRNA sequence derived from DNA, 5'
>HSERB2P	Human c-erb B2/neu protein gene, 5'end, and promoter region.
>HSERCC25	Human genomic and mRNA sequence for ERCC2 gene 5'region involved in
>HSERPA	Human erythropoietin gene, complete cds.
>HSERR	Human mRNA for oestrogen receptor
>HSESTEI1	H.sapiens exon 1 for elastase I
>HSFBRGG	Human gene for fibrinogen gamma chain
>HSFCERG5	Human lymphocyte IgE receptor gene 5'-region (Fc-epsilon R)
>HSFERG1	Human apoferritin H gene exon 1
>HSFIBBR1	Human fibrinogen beta gene 5' region and exon 1
>HSFIXG	Human factor IX gene, complete cds.
>HSFKBP1	Human FK506 binding proteins 12A, 12B and 12C (FKBP12) mRNA, exons
>HSFLAP1	Human 5-lipoxygenase activating protein (FLAP) gene, exon 1.
>HSFOS	Human fos proto-oncogene (c-fos), complete cds.
>HSGOS2PE	Human GOS2 gene, upstream region and cds.
>HSGCSFG	Human gene for granulocyte colony--stimulating factor (G-CSF)
>HSGEGR2	Human EGR2 gene 5' region 1233

>HSGHPROM	Human growth hormone (hGH) gene promoter
>HSGIPX1	Human gastric inhibitory polypeptide (GIP) mRNA, exon 1.
>HSGLA	Human GLA gene for alpha-D-galactosidase A (EC 3.2.1.22)
>HSGLUC1	Human glucagon gene transcription start region 732
>HSGMCSFG	Human gene for granulocyte-macrophage colony stimulating factor
>HSGR1	Human glucocorticoid receptor gene, exon 1. 1602
>HSGRFP1	Human growth hormone-releasing factor (GRF) gene, exon 1 (complete)
>HSGSTP15	Human GST pi gene for glutathione S-transferase pi exon 1 to 5
>HSGTRH	Human gene for gonadotropin-releasing hormone
>HSGYPC	Human glycophorin C (GPC) gene, exon 1, and promoter region.
>HSH10	Human histone (H10) gene, 5' flank.
>HSH1DNA	Human gene for H1 RNA 1057
>HSH1FNC1	Human H1 histone gene FNC16 promoter region
>HSH2B2H2	Human H2B.2 and H2A.1 genes for Histone H2A and H2B
>HSH4AHIS	H.sapiens H4/a gene for H4 histone
>HSH4BHIS	H.sapiens H4/b gene for H4 histone
>HSHARA	Human androgen receptor gene, transcription initiation sites.
>HSHCG5B1	Human chorionic gonadotropin (hCG) beta subunit gene 5 5'-flank
>HSHEMPRO	Human DNA for hemopoxin promoter
>HSHIAPPA	Human islet amyloid polypeptide (hIAPP) gene, complete cds.
>HSHIH4	Human H4 histone gene

>HSHISH2A	Human histone H2a gene
>HSHISH2B	Human histone H2b gene
>HSHISH3	Human histone H3 gene
>HSHLAA1	Human HLA-A1 gene
>HSHLAB27	Human gene for HLA-B27 antigen
>HSHLABW	Human HLA-Bw57 gene
>HSHLAF	Human HLA-F gene for human leukocyte antigen F
>HSHLIA	Human gene for histocompatibility antigen HLA-A3
>HSHLIC	Human gene for class I histocompatibility antigen HLA-CW3
>HSHMG17G	Human HMG-17 gene for non-histone chromosomal protein HMG-17
>HSHOX3D	Human HOX3D gene for homeoprotein HOX3D
>HSHSC70	Human hsc70 gene for 71 kd heat shock cognate protein
>HSHSP70D	Human heat shock protein (hsp 70) gene, complete cds.
>HSHSP70P	Human hsp70B gene 5'-region
>HSIAPP12	Human IAPP gene exon 1 and exon 2 for islet amyloid polypeptide
>HSICAMAB	Human intercellular adhesion molecule 1 (ICAM-1) gene, exon 1.
>HSIFI54	Human interferon-inducible gene IFI-54K 5'flank
>HSIFNA14	Human interferon alpha gene IFN-alpha 14
>HSIFNA16	Human interferon alpha gene IFN-alpha 16
>HSIFNA5	Human interferon alpha gene IFN-alpha 5
>HSIFNA6	Human interferon alpha gene IFN-alpha 6
>HSIFNA7	Human interferon alpha gene IFN-alpha 7

>HSIFNG	Human immune interferon (IFN-gamma) gene.
>HSIFNIN6	Human alpha/beta-interferon(IFN)-inducible 6-16 gene exon 1 and
>HSIGF24B	Human DNA for insulin-like growth factor II (IGF-2); exon 4B
>HSIGFBP1A	Human insulin-like growth factor binding protein (hIGFBP1) gene
>HSIGK10	Human germline gene for the leader peptide and variable region
>HSIGK15	Human germline gene for the leader peptide and variable region
>HSIGK17	Human rearranged gene for kappa immunoglobulin subgroup V kappa IV
>HSIGK20	Human rearranged DNA for kappa immunoglobulin subgroup V kappa III
>HSIGKLC1	Human germline fragment for immunoglobulin kappa light chain
>HSIGVA5	Human germline immunoglobulin kappa light chain V-segment
>HSIL05	Human interleukin-2 (IL-2) gene and 5'-flanking region
>HSIL1AG	Human gene for interleukin 1 alpha (IL-1 alpha)
>HSIL1B	Human gene for prointerleukin 1 beta
>HSIL2RG1	Human interleukin 2 receptor gene 5' flanking region and exon 1
>HSIL45	Human interleukin 4 gene 5'-region
>HSIL5	Human interleukin 5 (IL-5) gene, complete cds.
>HSIL6B	Human interleukin 6 (IL 6) gene, 5' flank.
>HSIL71	Human interleukin 7 (IL7) gene, exon 1.
>HSIL9A	Human IL9 protein gene, complete cds.

>HSINSU	Human gene for preproinsulin, from chromosome 11. Includes a highly
>HSINT1G	Human int-1 mammary oncogene
>HSJUNCAA	Human jun-B gene, complete cds.
>HSKER65A	Human DNA for 65 kD keratin type II exon 1 and 5′ flank
>HSKERUHS	Human gene for ultra high-sulphur keratin protein
>HSLACTG	Human alpha-lactalbumin gene
>HSLAG1G	Human LAG-1 gene
>HSLCATG	Human gene for lecithin-cholesterol acyltransferase (LCAT)
>HSLCK1	Human lymphocyte-specific protein tyrosine kinase (lck) gene
>HSLFACD	Human leukocyte function-associated antigen-1 (LFA-1 or CD11a)
>HSLPLA	Human lipoprotein lipase (LPL) gene, 5′ flank.
>HSLYAM01	Human leukocyte adhesion molecule-1 (LAM-1), exon 1.
>HSLYSOZY	Human lysozyme gene (EC 3.2.1.17)
>HSMBP1A	Human DNA for mannose binding protein 1 (MBP1), Exon 1
>HSMCCPAA	Human mast cell carboxypeptidase A (MC-CPA) gene, exons 1-2.
>HSMDR1	Human P-glycoprotein (MDR1) mRNA, complete cds.
>HSMED	Human bone marrow serine protease gene (medullasin)
>HSMEHG	Human DNA (exon 1) for microsomal epoxide hydrolase
>HSMETIE	Human metallothionein-Ie gene (hMT-Ie).
>HSMG01	Human myoglobin gene (exon 1)
>HSMGSAG	Human gene for melanoma growth stimulatory activity (MGSA)

>HSMHCAG1	Human alpha-MHC gene for myosin heavy chain N-terminus)
>HSMHCGE1	Human class II invariant gamma-chain gene (5' flank, exon 1)
>HSMHCW5	Human MHC class I HLA-Cw5 gene, 5' flank.
>HSMLN1	Human motilin gene exon 1
>HSMPOA	Human myeloperoxidase gene, exons 1-4.
>HSMRP	Human mitochondrial RNA-processing endoribonuclease RNA (mrp) gene
>HSMTS1A	H.sapiens mts1 gene, 5' end.
>HSMYCE12	Human myc-oncogene exon 1 and exon 2
>HSNAKATP	Human Na,K-ATPase beta subunit (ATP1B) gene, exons 1 and 2.
>HSNEURK1	H.sapiens gene for neuromedin K receptor (exon 1)
>HSNFH1	Human gene for heavy neurofilament subunit (NF-H) exon 1
>HSNFIL6	Human gene for nuclear factor NF-IL6
>HSNFLG	Human gene for neurofilament subunit NF-L
>HSNK21	Human neurokinin-2 receptor (NK-2) gene, exon 1.
>HSNMYC	Human germ line n-myc gene
>HSNRASPR	H. sapiens N-RAS promoter region
>HSODC1A	Human ornithine decarboxylase (ODC1) gene, complete cds.
>HSOTCEX1	Human ornithine transcarbamylase (OTC) gene, 5'-end region.
>HSOTNPI	Human prepro-oxytocin-neurophysin I gene, complete cds.
>HSP450SCC	Human cytochrome P450scc gene, 5' end and promoter region.
>HSP53G	Human p53 gene for transformation related protein p53

>HSPADP	Human promoter DNA for Alzheimer's disease amyloid A4 precursor
>HSPAI11	Human gene for plasminogen activator inhibitor 1 (PAI-1) 5'-flank
>HSPGDF	Human platelet-derived growth factor A-chain (PDGF) gene, 5' end
>HSPGP95G	Human PGP9.5 gene for neuron-specific ubiquitin C-terminal
>HSPLSM	Human plasminogen gene, exon 1.
>HSPNMTB	Human gene for phenylethanolamine N-methylase (PNMT) (EC 2.1.1.28)
>HSPOMC5F	Human opiomelanocortin gene, 5' flank.
>HSPP14B	Human placental protein 14 (PP14) gene, complete cds.
>HSPRB3L	Human gene PRB3L for proline-rich protein G1
>HSPRB4S	Human PRB4 gene for proline-rich protein Po, allele S
>HSPRLNC	Human prolactin mRNA, partial cds.
>HSPROAA1	Human prothymosin-alpha gene, complete cds.
>HSPROT2	Human protamine 2 gene, complete cds.
>HSPRPE1	Human SPR2-1 gene for small proline rich protein (exon 1)
>HSPS2G1	Human estrogen-responsive gene pS2 5'flank and exon 1
>HSPSAP	Human pulmonary surfactant apoprotein (PSAP) gene, complete cds.
>HSPSP94A	Human gene for prostatic secretory protein PSP-94, exon 1
>HSPTHRPA	Human parathyroid hormone-related peptide (PTHRP) gene, exons 1A,
>HSPURNPHO	Human gene for purine nucleoside phosphorylase (upstream region)
>HSRDNA	Human rDNA origin of transcription

>HSREGA01	Human regenerating protein (reg) gene, complete cds.
>HSREN01	Human renin gene 5' region and exon 1
>HSRPBG1	Human gene fragment for retinol binding protein (RBP) (exon 1-4)
>HSSAA1A	Human serum amyloid A (GSAA1) gene, complete cds.
>HSSAA1B	H.sapiens SAA1 beta gene
>HSSB4B1	Human gene fragment for HLA class II SB 4-beta chain (exon 1)
>HSSISG5	Human c-sis proto-oncogene 5' region
>HSSLIPG	Human SLPI gene for secretory leukocyte protease inhibitor
>HSSOD1G1	Human superoxide dismutase (SOD-1) gene exon 1 and 5' flanking
>HSSODB	Human ornithine decarboxylase gene, complete cds.
>HSSRDA01	H.sapiens steroid 5-alpha-reductase gene, exon 1.
>HSSUBP1G	H.sapiens gene for substance P receptor (exon 1)
>HSSYB1A1	Human synaptobrevin 1 (SYB1) gene, exon 1.
>HSTAT1	Human gene for tyrosine aminotransferase (TAT) (EC 2.6.1.5) Exon 1.
>HSTCBV81	Human T-cell receptor V-beta 8.1 gene 775
>HSTCRB21	Human T-cell receptor beta chain gene variable region.
>HSTFG5	Human transferrin (Tf) gene 5'region
>HSIL3FL5	Human interleukin 3 gene, 5' flank.
>HSTFPB	Human tissue factor gene, complete cds.
>HSTGFB1	Human mRNA for transforming growth factor-beta (TGF-beta)

>HSTGFB3B	Human transforming growth factor beta-3 gene, 5' end.
>HSTGFBET2	Human transforming growth factor beta-2 gene, 5' end.
>HSTH01	Human tyrosine hydroxylase (TH) (EC 1.14.16.2) gene from upstream
>HSTHIO2A	Human metallothionein gene IIA promoter region
>HSTHRO01	Human thrombospondin gene, exons 1, 2 and 3.
>HSTHXBG	H.sapiens gene for thyroxine-binding globulin gene
>HSTHYR5	Human thyroglobulin gene 5' region
>HSTNFA	Human gene for tumor necrosis factor (TNF-alpha)
>HSTNFB	Human gene for lymphotoxin (TNF-beta)
>HSTOP01	Homo sapiens type I DNA topoisomerase gene, exons 1 and 2.
>HSTPIA	Human triosephosphate isomerase (TPI) gene, 5' end.
>HSTPO5	Human thyroid peroxidase gene 5'end (EC 1.11.1.7)
>HSTRP	Human transferrin receptor gene promoter region
>HSTRPY1B	Human tryptase-I gene, complete cds.
>HSTUBB2	Human beta 2 gene for beta-tubulin
>HSTYRO1E	Human tyrosinase gene, exon 1 and 5' flanking region (EC 1.14.18.1)
>HSU6RNA	Human gene for U 6 RNA
>HSUPA	Human uPA gene for urokinase-plasminogen activator
>HSVAVPO1	Human proto-oncogene vav, 5' end.
>HSVCAM1A	Human vascular cell adhesion molecule-1 (VCAM1) gene, complete CDS.

>HSVIM5RR	Human vimentin gene 5' regulatory region

Once the gene target or, in the case of small pathogens, the genome target has been identified, short sequences within the gene or genome target are identified as medically significant target sites. Medically significant target sites can be defined as short DNA sequences (approximately 4-30 base pairs) that are required for the expression or replication of genetic material. For example, sequences that bind regulatory factors, either transcriptional or replicatory factors, are ideal target sites for altering gene or viral expression.

Further, coding sequences may be adequate target sites for disrupting gene function, although the disruption of a polymerase complex that is moving along the DNA sequence may require a stronger binder than for the disruption of the initial binding of a regulatory protein.

Finally, even non-coding, non-regulatory sequences may be of interest as target sites (e.g., for disrupting replication processes or introducing an increased mutational frequency).

Several specific examples of medically significant target sites are shown in Table IV.

Table IV

MEDICALLY SIGNIFICANT DNA-BINDING SEQUENCES

Test sequence	DNA-binding Protein	Medical Significance
EBV origin of replication	EBNA	infectious mononucleosis, nasal pharyngeal carcinoma
HSV origin of replication	UL9	oral and genital Herpes

Test sequence	DNA-binding Protein	Medical Significance
VZV origin of replication	UL9-like	shingles
HPV origin of replication	E2	genital warts, cervical carcinoma
Interleukin 2 enhancer	NFAT-1	immunosuppressant
HIV LTR	NFAT-1 NFkB	AIDS, ARC
HBV enhancer	HNF-1	hepatitis
Fibrogen promoter	HNF-1	cardiovascular disease
Oncogene promoter and coding sequences	??	cancer

(Abbreviations: EBV, Epstein-Barr virus; EBNA, Epstein-Barr virus nuclear antigen; HSV, Herpes Simplex virus; VZV, Varicella zoster virus; HPV, human papilloma virus; HIV LTR, Human immunodeficiency virus long terminal repeat; NFAT, nuclear factor of activated T cells; NFkB, nuclear factor kappaB; AIDS acquired immune deficiency syndrome; ARC, AIDS related complex; HBV, hepatitis B virus; HNF, hepatic nuclear factor.)

For example, origin of replication binding proteins have short, well-defined binding sites within the viral genome and are therefore excellent target sites for a competitive DNA-binding drug. Examples of such proteins include, Epstein Barr virus nuclear antigen 1 (EBNA-1) (Ambinder, *et al.*; Reisman, *et al.*), E2 (which is encoded by the human papilloma virus) (Chin, *et al.*), UL9 (which is encoded by herpes simplex virus type 1) (McGeoch, *et al.*), and the homologous protein in varicella zoster virus (VZV) (Stow, *et al.*).

Similarly, recognition sequences for DNA-binding proteins that act as transcriptional regulatory factors

are also good target sites for antiviral DNA-binding drugs. Examples listed in Table IV include (i) the binding site for hepatic nuclear factor (HNF-1), which is required for the expression of human hepatitis B virus (HBV) (Chang), and (ii) NFκB and NFAT-1 binding sites in the human immunodeficiency virus (HIV) long terminal repeat (LTR), one or both of which may be involved in the expression of the virus (Greene, W.C.).

Examples of non-viral DNA targets for DNA-binding drugs are also shown in Table IV to illustrate the wide range of potential applications for sequence-specific DNA-binding molecules. For example, nuclear factor of activated T cells (NFAT-1) is a regulatory factor that is crucial to the inducible expression of the interleukin 2 gene in response to signals from the antigen receptor, which, in turn, is required for the cascade of molecular events during T cell activation (for review, see Edwards, C.A., and Crabtree, G.R.). The mechanism of action of two immunosuppressants, cyclosporin A and FK506, is thought to be to block the inducible expression of NFAT-1 (Schmidt, *et al.* and Banerji, *et al.*). However, the effects of these drugs are not specific to NFAT-1; therefore, a drug targeted specifically to the NFAT-1 binding site in the IL-2 enhancer would be desirable as an improved immunosuppressant.

Targeting the DNA site with a DNA-binding drug rather than targeting with a drug that affects the DNA-binding protein (presumably the target of the current immunosuppressants) is advantageous for at least two reasons: first, there are many fewer target sites for specific DNA sequences than specific proteins (*e.g.*, in the case of glucocorticoid receptor, a handful of DNA-binding sites vs. about 50,000 protein molecules in each cell); and second, only the targeted gene need be

affected by a DNA-binding drug, while a protein-binding drug would disable all the cellular functions of the protein. An example of the latter point is the binding site for HNF-1 in the human fibrinogen promoter. Fibrinogen level is one of the most highly correlated factor with cardiovascular disease. A drug targeted to either HNF-1 or the HNF-1 binding site in the fibrinogen promoter might be used to decrease fibrinogen expression in individuals at high risk for disease because of the over-expression of fibrinogen. However, since HNF-1 is required for the expression of a number of normal hepatic genes, blocking the HNF-1 protein would be toxic to liver function. In contrast, by blocking a DNA sequence that is composed in part of the HNF-1 binding site and in part by flanking sequences for divergence, the fibrinogen gene can be targeted with a high level of selectivity, without harm to normal cellular HNF-1 functions.

The assay has been designed to screen virtually any DNA sequence. Test sequences of medical significance include viral or microbial pathogen genomic sequences and sequences within or regulating the expression of oncogenes or other inappropriately expressed cellular genes. In addition to the detection of potential antiviral drugs, the assay of the present invention is also applicable to the detection of potential drugs for (i) disrupting the metabolism of other infectious agents, (ii) blocking or reducing the transcription of inappropriately expressed cellular genes (such as oncogenes or genes associated with certain genetic disorders), and (iii) the enhancement or alteration of expression of certain cellular genes.

2. Defined Sets of Test Sequences.

The approach described in the above section emphasizes screening large numbers of fermentation broths, extracts, or other mixtures of unknowns against specific medically significant DNA target sequences. The assay can also be utilized to screen a large number of DNA sequences against known DNA-binding drugs to determine the relative affinity of the single drug for every possible defined specific sequence. For example, there are 4^n possible sequences, where n = the number of nucleotides in the sequence. Thus, there are 4^3 = 64 different three base pair sequences, 4^4 = 256 different four base pair sequences, 4^5 = 1024 different 5 base pair sequences, etc. If these sequences are placed in the test site, the site adjacent to the screening sequence (the example used in this invention is the UL9 binding site), then each of the different test sequences can be screened against many different DNA-binding molecules.

The test sequences may be placed on either or both sides of the screening sequence, and the sequences flanking the other side of the test sequences are fixed sequences to stabilize the duplex and, on the 3′ end of the top strand, to act as an annealing site for the primer (see Example 1). In Figure 14B, the TEST and SCREENING sequences are indicated. The preparation of such double-stranded oligonucleotides is described in Example 1 and illustrated in Figure 4.

The test sequences, denoted in Figure 14B as X:Y (where X = A,C,G, or T and Y = the complementary sequence, T,G,C, or A), may be any of the 256 different 4 base pair sequences shown in Figure 13.

Once a set of test oligonucleotides containing all possible four base pair sequences has been synthesized (see Example 1), the set can be screened with any DNA-

binding drug. The relative effect of the drug on each oligonucleotide assay system will reflect the relative affinity of the drug for the test sequence. The entire spectrum of affinities for each particular DNA sequence can therefore be defined for any particular DNA-binding drug. This data, generated using the assay of the present invention, can be used to facilitate molecular modeling programs and/or be used directly to design new DNA-binding molecules with increased affinity and specificity.

Another type of ordered set of oligonucleotides that may be useful for screening are sets comprised of scrambled sequences with fixed base composition. For example, if the recognition sequence for a protein is 5'-GATC-3' and libraries were to be screened for DNA-binding molecules that recognized this sequence, then it would be desirable to screen sequences of similar size and base composition as control sequences for the assay. The most precise experiment is one in which all possible 4 bp sequences are screened. In the case of a 4 base-pair sequence, this represents $4^4 = 256$ different test sequences: a number of screening sequences that may not be practical in every situation. However, there are many fewer possible 4 bp sequences with the same base composition (1G, 1A, 1T, 1C) ($n! = 24$ different 4 bp sequences with this particular base composition), such sequences provide excellent controls without having to screen large numbers of sequences.

3. <u>Theoretical Considerations in Choosing Biological Target Sites: Specificity and Toxicity</u>.

One consideration in choosing sequences to screen using the assay of the present invention is test

sequence accessibility, that is, the potential exposure of the sequence *in vivo* to binding molecules. Cellular DNA is packaged in chromatin, rendering most sequences relatively inaccessible. Sequences that are actively transcribed, particularly those sequences that are regulatory in nature, are less protected and more accessible to both proteins and small molecules. This observation is substantiated by a large literature on DNAase I sensitivity, footprinting studies with nucleases and small molecules, and general studies on chromatin structure (Tullius). The relative accessibility of a regulatory sequence, as determined by DNAase I hypersensitivity, is likely to be several orders of magnitude greater than an inactive portion of the cellular genome. For this reason the regulatory sequences of cellular genes, as well as viral regulatory or replication sequences, are useful regions to choose for selecting specific inhibitory small molecules using the assay of the present invention.

Another consideration in choosing sequences to be screened using the assay of the present invention is the uniqueness of the potential test sequence. As discussed above for the nuclear protein HNF-1, it is desirable that small inhibitory molecules are specific to their target with minimal cross reactivity. Both sequence composition and length effect sequence uniqueness. Further, certain sequences are found less frequently in the human genome than in the genomes of other organisms, for example, mammalian viruses. Because of base composition and codon utilization differences, viral sequences are distinctly different from mammalian sequences. As one example, the dinucleotide CG is found much less frequently in mammalian cells than the dinucleotide sequence GC: further, in SV40, a mammalian virus, the sequences A<u>GC</u>T and A<u>CG</u>T

are represented 34 and 0 times, respectively. Specific viral regulatory sequences can be chosen as test sequences keeping this bias in mind. Small inhibitory molecules identified which bind to such test sequences will be less likely to interfere with cellular functions.

There are approximately 3×10^9 base pairs (bp) in the human genome. Of the known DNA-binding drugs for which there is crystallographic data, most bind 2-5 bp sequences. There are $4^4 = 256$ different 4 base sequences; therefore, on average, a single 4 bp site is found roughly 1.2×10^7 times in the human genome. An individual 8 base site would be found, on average, about 50,000 times in the genome. On the surface, it might appear that drugs targeted at even an 8 bp site might be deleterious to the cell because there are so many binding sites; however, several other considerations must be recognized.

First, most DNA is tightly wrapped in chromosomal proteins and is relatively inaccessible to incoming DNA-binding molecules as demonstrated by the nonspecific endonucleolytic digestion of chromatin in the nucleus (Edwards, C.A. and Firtel, R.A.). Active transcription units are more accessible, but the most highly exposed regions of DNA in chromatin are the sites that bind regulatory factors. As demonstrated by DNAase I hypersensitivity (Gross, D.S. and Garrard, W.T.), regulatory sites may be 100-1000 times more sensitive to endonucleolytic attack than the bulk of chromatin. This is one reason for targeting regulatory sequences with DNA-binding drugs.

Secondly, several anticancer drugs that bind 2, 3, or 4 bp sequences have sufficiently low toxicity so that they can be used as drugs. This indicates that, if high affinity binding sites for known drugs can be

matched with specific viral target sequences, it may be possible to use currently available drugs as antiviral agents at lower concentrations than they are currently used, with a concomitantly lower toxicity.

4. <u>Further Considerations in Choosing Target Sites: Finding Eukaryotic Promoters</u>.

Eukaryotic organisms have three RNA polymerases (Pol I, II, and III) that transcribe genetic information from DNA to RNA. The correct regulation of this information flow is essential for the survival of the cell. These multi-subunit enzymes need additional proteins to regulate transcription. Many of these additional proteins bind to DNA in a region 5′ of the translation start site for a gene: this region is generally known as the promoter region of the gene.

All three polymerases use a core set of general transcription proteins to bind to this region. A central component of this complex is the protein called TBP or TFIID. The site this protein binds to is known as the TATA-box because the sequence usually contains a sequence motif similar to TATA (*e.g.*, TATAa/tAa/t). Originally it was thought that each of the three polymerases used a separate set of general transcription factors and that Pol II used TFIID exclusively. Recently it has been shown that all three classes of RNA polymerase need TFIID for transcriptional regulation (see Comai, *et al.*; and Greenblatt)

A molecule that binds to a DNA sequence closely adjacent or overlapping a TATA binding site will likely alter transcriptional regulation of the gene. If the molecule binds based solely on specificity to the TATA-box sequence itself, then this molecule is expected to be very toxic to cells since the transcription of most

genes would be altered. The sequences adjacent to TATA boxes, however, are not conserved. Accordingly, if a particular sequence is selected adjacent a TATA box of a particular gene, a molecule that binds to this specific sequence would be expected to alter the transcriptional regulation of just that gene.

TATA-boxes were first identified by determining the sequence of the DNA located 5′ of the RNA start sites of a number of genes. Examination of these sequences revealed that most genes had a TATA-box motif (consensus sequence) in the range of nucleotides 50 to 15 nucleotides 5′ of the RNA start site. *In vitro* studies, typically DNA protection (footprinting) studies, lead to the conclusion that proteins were binding to these sites. Further *in vitro* DNA binding experiments demonstrated that some proteins could specifically bind to these sites. This lead to assays that allowed purification and subsequent sequencing of the binding proteins. This information facilitated the cloning and expression of genes encoding the binding proteins. A large number of transcription factors are now known. The protein designated TFIID has been demonstrated to bind to the TATA-box (Lee, *et al.*).

Molecules that interfere with the interaction of these transcription factors and their target DNA (*i.e.*, DNA/Protein transcription complexes) are also expected to alter transcription initiated from the target DNA. A publicly available database of these factors and the sequences to which they bind is available from the National Library of Medicine and is called "The Transcription Data Base, or TFD." The binding sites of these transcription factors can be identified in the 5′ non-coding region of genes having known sequences (Example 15).

The ability to select target sequences adjacent the binding site of a transcription factor, as described above for TFIID, can be applied to other general transcription factors as well. For the purpose of the present invention, a general transcription factor is one that regulates the transcriptional expression of more than one gene. For any such general transcription factor, as for TFIID above, a particular target sequence can be selected adjacent the transcription factor binding site of a selected gene. A molecule that binds to this specific target sequence would be expected to alter the transcriptional regulation of just that gene and not all of the genes for which the transcription factor regulates expression. Alteration of transcriptional regulation may involve inhibition or increased affinity (enhancement) of binding of a transcription factor to its cognate DNA.

Many examples of such general transcription factors have been identified, including, but not limited to, the following: SP1 (Raney, *et al.*, 1992; Kitadai, *et al.*, 1992); NFAT-1 (Shaw, et al., 1988); Ets family of transcription factors, including Elf1 (Thompson, *et al.*, 1992); Fos protein (Neuberg, *et al.*, 1991); NF-kappa (Wirth, *et al.*, 1988; Meijer, *et al.*, 1992); and AP1-like proteins, including the product of the c-jun oncogene (Descheemaeker, *et al.*, 1992; Ryder et al., 1988; Harshman et al., 1988; Angel et al., 1988; Bos et al., 1988; Bohmann et al., 1987).

Accordingly, for a selected gene, non-conserved DNA surrounding the transcription factor binding site can be chosen as a specific target sequence for small molecule binding. A small molecule can be chosen whose binding overlaps an adjacent transcription factor DNA binding sequence (*e.g.*, by 1-3 nucleotide pairs). In this case, the specificity of DNA binding for the small

molecule is, in large part, derived from the non-conserved sequences adjacent the transcription factor binding site, in order to reduce small molecule binding at the transcription factor binding site associated with other genes.

Small molecules that bind such specific target sequences can be identified and/or designed using the assay and methods of the present invention.

5. Further Considerations in Choosing Alternative Small-Molecule-Binding Target Sites.

Small molecules that interfere with the interaction of any DNA binding protein and its cognate DNA (*i.e.*, DNA/Protein complexes) can be selected by the assay and methods of the present invention. As described above for general transcription factors, sequences adjacent the DNA binding site for a selected DNA binding protein can serve as a target for small molecule binding in order to alter the interaction of the DNA binding protein and its cognate site. The small molecule can affect the DNA:protein interaction, for example, by inhibiting or enhancing the association of protein with the DNA.

For a selected DNA:protein interaction, non-conserved DNA surrounding the selected DNA binding site can be chosen as a specific target sequence for small molecule binding. In some cases the small molecule binding can overlap the DNA binding site: for example, in the case of a therapeutic used to treat a mammal with a bacterial infection, a small molecule may be selected to bind to the bacterial origin of DNA replication. Such a small molecule may essentially completely overlap the region defined by the bacterial origin-of-replication-DNA:protein interaction since a

corresponding target sequence is not likely present in the DNA of the mammalian host.

However, in the case where selective binding is required, as described above for TFIID, the specificity of the small molecule for DNA binding should essentially derive from the non-conserved sequences adjacent the DNA-binding protein's cognate DNA-binding site. This results in small molecule binding being reduced at similar DNA:protein binding sites at other locations.

6. Further Considerations in Choosing Target Sites: Procaryotes and Viruses.

Bacterial gene expression is regulated at several different levels, including transcription. General and specific transcription factors are needed along with the core RNA polymerase to accurately produce appropriate amounts of mRNA. Antibiotics that bind to the RNA polymerase and prevent mRNA production are potent bacterial poisons: molecules that could interfere with the initiation of transcription for specific essential genes are expected to have similar effects.

Many bacterial promoters have been sequenced and carefully examined. In general, the majority of bacterial promoters have two well characterized regions, the -35 region which has a consensus sequence similar to SEQ ID NO:625 and the -10 region with a consensus sequence of SEQ ID NO:626. The sequence of the start site for RNA polymerase, however, is not always the same. The start site is determined by a supplementary protein called the sigma factor, which confers specificity for binding the RNA polymerase core. Several sigma factors are present in any species of bacteria. Each sigma factor recognizes a different set of promoter sequences. Expression of sigma factors

is regulated, typically, by the growth conditions the bacteria is encountering. These sigma factor promoter sequences represent excellent targets for sequence specific DNA binding molecules.

As an example of choosing target sequences for the purpose of designing a DNA-binding therapeutic for a bacterial disease, consider the example of tuberculosis. Tuberculosis is caused by *Mycobacterium tuberculosis*.

All bacteria need to make ribosomes for the purpose of protein synthesis. The -35 and -10 regions of *M. tuberculosis* ribosome RNA synthesis has been determined. In the EMBL locus MTRRNOP the -35 signal is located at coordinants 394..400 and the -10 signal is found at coordinants 419..422. These regions represent excellent targets for a DNA binding drug that would inhibit the growth of the bacteria by disrupting its ability to make ribosomes and synthesize protein. Multiple other essential genes could be targeted in a similar manner.

M. tuberculosis is a serious public health problem for several reasons, including the development of antibiotic resistant strains. Many antibiotics inhibit the growth of bacteria by binding to a specific protein and inhibiting its function. An example of this is the binding of rifampicin to the beta subunit of the bacterial RNA polymerase. Continued selection of bacteria with an agent of this kind can lead to the selection of mutants having an altered RNA polymerase so that the antibiotic can no longer bind it. Such mutants can arise from a single mutation.

However, binding a drug to a DNA regulatory region requires at least two mutations to escape the inhibitory effect of the drug: one mutation in the target DNA sequence so that the drug could not bind the target se-

quence, and one mutation in the regulatory binding protein so that it can recognize the new, mutated regulatory sequence. Such a double mutation event is much less frequent than the single mutation discussed above, for example, with rifampicin. Accordingly, it is expected that the development of drug resistant bacteria would be much less common for DNA-binding drugs that bind to promoter sequences.

The HIV viral promoter region (shown in Figure 28) provides an example of choosing DNA target sequences for sequence-specific DNA binding drugs to inhibit viral replication.

Many eukaryotic viruses use promoter regions that have similar features to normal cellular genes. The replication of these viruses depends on the general transcription factors present in the host cell. As such, the promoter sequences in DNA viruses are similar to those found in cellular genes and have been well-studied. The binding factors Sp-1 and TFIID are important generalized factors that most viral promoters use.

In the HIV promoter sequence found in LOCUS HIVBH101 in version 32 of the EMBL databank, three tandem decanucleotide Sp1 binding sites are located between positions 377 and 409. Site III shows the strongest affinity for the cellular factor. The three cause up to a tenfold effect on transcriptional efficiency in vitro. The transcription start site is at position 455, with a TATA box at 427-431 in the sequence listed below. In addition to these sites, there are two NF-kappa-B sites in this region between nucleotides 350 and 373. These sites are annotated in Figure 28.

Sequence-specific DNA binding molecules that specifically disrupted this binding would be expected

to disrupt HIV replication. For example, the sequences adjacent to the TFIID binding site (SEQ ID NO:628 and/or SEQ ID NO:629), would be target sites for a DNA-binding molecule designed to disrupt TFIID binding. These sequences are found in HIV but are not likely to occur overlapping TFIID binding sites in the endogenous human genome. Multiple sites could be targeted to decrease the likelihood that a single mutation could prevent drug binding.

D. Using Test Matrices and Pattern Matching for the Analysis of Data.

The assay described herein has been designed to use a single DNA:protein interaction to screen for sequence-specific and sequence-preferential DNA-binding molecules that can recognize virtually any specified sequence. By using sequences flanking the recognition site for a single DNA:protein interaction, a very large number of different sequences can be tested. The analysis of data yielded by such experiments displayed as matrices and analyzed by pattern matching techniques should yield information about the relatedness of DNA sequences.

The basic principle behind the DNA:protein assay of the present invention is that when molecules bind DNA sequences flanking the recognition sequence for a specific protein the binding of that protein is blocked. Interference with protein binding likely occurs by either (or both) of two mechanisms: (i) directly by stearic hindrance, or (ii) indirectly by perturbations transmitted to the recognition sequence through the DNA molecule.

Both of these mechanisms will presumably exhibit distance effects. For inhibition by direct stearic hindrance direct data for very small molecules is

available from methylation and ethylation interference studies. These data suggest that for methyl and ethyl moieties, the stearic effect is limited by distance effects to 4-5 base pairs. Even still the number of different sequences that can theoretically be tested for these very small molecules is still very large (*i.e.*, 5 base pair combinations total 4^5 (=1024) different sequences).

In practice, the size of sequences tested can be explored empirically for different sized test DNA-binding molecules. A wide array of sequences with increasing sequence complexity can be routinely investigated. This may be accomplished efficiently by synthesizing degenerate oligonucleotides and multiplexing oligonucleotides in the assay process (*i.e.*, using a group of different oligonucleotides in a single assay) or by employing pooled sequences in test matrices.

In view of the above, assays employing a specific protein and oligonucleotides containing the specific recognition site for that protein flanked by different sequences on either side of the recognition site can be used to simultaneously screen for many different molecules, including small molecules, that have binding preferences for individual sequences or families of related sequences. Figure 12 demonstrates how the analysis of a test matrix yields information about the nature of competitor sequence specificity. As an example, to screen for molecules that could preferentially recognize each of the 256 possible tetranucleotide sequences (Figure 13), oligonucleotides could be constructed that contain these 256 sequences immediately adjacent to a 11 bp recognition sequence of UL9 *oriS* SEQ ID NO:615, which is identical in each construct.

In Figure 12 "+" indicates that the mixture retards or blocks the formation of DNA:protein complexes in solution and "-" indicates that the mixture had no marked effect on DNA:protein interactions. The results of this test are shown in Table V.

Table V

Test Mix	Specificity
#1,4,7: oligos	none detected for the above
#2: for recognition site	either nonspecific or specific
#3	AGCT
#5	CATT or ATT
#6	GCATTC, GCATT, CATTC, GCAT, or ATTC
#8	CTTT

These results demonstrate how such a matrix provides data on the presence of sequence specific binding activity is a test mixture and also provides inherent controls for non-specific binding. For example, the effect of test mix #8 on the different test assays reveals that the test mix preferentially affects the oligonucleotides that contain the sequence CCCT. Note that the sequence does not have to be within the test site for test mix #8 to exert an affect. By displaying the data in a matrix, the analysis of the sequences affected by the different test mixtures is facilitated.

Furthermore, defined, ordered sets of oligonucleotides can be screened with a chosen DNA-binding molecule. The results of these binding assays can then be examined using pattern matching techniques to determine the subsets of sequences that bind the molecule with similar binding characteristics. If the structural and

biophysical properties (such as, geometric shape and electrostatic properties) of sequences are similar, then it is likely that they will bind the molecule with similar binding characteristics. If the structural and biophysical properties of sequences are different, then it is likely that they will not bind the molecule with similar binding characteristics. In this context, the assay might be used to group defined, ordered sequences into subsets based on their binding characteristics: for example, the subsets could be defined as high affinity binding sites, moderate affinity binding sites, and low affinity binding sites. Sequences in the subsets with positive attributes (e.g., high affinity binding) have a high probability of having similar structural and biophysical properties to one another.

By screening and analyzing the binding characteristics of a number of DNA-binding molecules against the same defined set of DNA sequences, data can be accumulated about the subsets of sequences that fall into the same or similar subsets. Using this pattern matching approach, which can be computer-assisted, the sequences with similar structural and biophysical properties can by grouped empirically.

The database arising from pattern matching analysis of raw assay data will lead to the increased understanding of sequence structure and thereby lead to the design of novel DNA-binding molecules with related but different binding activities.

E. Applications for the Determination of the Sequence Specificity of DNA-Binding Drugs.

Applications for the determination of the sequence specificity of DNA-binding drugs are described below. The applications are divided into drug homo- and

heteromeric polymers (part 1) and sequence-specific DNA-binding molecules as facilitators of triple strand formation (part 2).

One utility of the assay of the invention is the identification of highest affinity binding sites among all possible sites of a certain length for a given DNA-binding molecule. This information may be valuable to the design of new DNA-binding therapeutics.

1. <u>Multimerization of Sequence-Preferential or Sequence-Specific DNA-Binding Molecules Identified in the Assay</u>.

Any particular DNA-binding small molecule screened in the assay may only recognize a 2-4 base pair site, and even if the recognition is quite specific, the molecule may be toxic because there are so many target sites in the genome ($3 \times 10^9/4^4$ 4 bp sites, for example). However, if drugs with differential affinity for different sites are identified, the toxicity of DNA-binding drugs may be drastically reduced by creating dimers, trimers, or multimers with these drugs (Example 13). From theoretical considerations of the free energy changes accompanying the binding of drugs to DNA, the intrinsic binding constant of a dimer should be the square of the binding constant of the monomer (Le Pecq, J.B.). Experimental data confirmed this expectation in 1978 with dimer analogs of ethidium bromide (Kuhlmann, *et al.*). Dimerization of several intercalating molecules, in fact, yields compounds with DNA affinities raised from 10^5 M^{-1} for the corresponding monomer to 10^8 to 10^9 M^{-1} for the dimers (Skorobogaty, *et al.*; Gaugain, *et al.* (1978a and b); Le Pecq, *et al.*; Pelaprat, *et al.*). Trimerization, which theoretically should yield binding affinities that are the cube of the affinity of the

homomonomeric subunit or the product of affinities of the heteromonomeric subunits, has yielded compounds with affinities as high as $10^{12}M^{-1}$ (Laugaa, *et al.*). Such affinity is markedly better than the affinities seen for many DNA regulatory proteins.

As a hypothetical example, if a relatively weak DNA-binding drug, drug X, which binds a 4 bp site with an affinity of $2 \times 10^5 M^{-1}$ was dimerized, the bis-X drug would now recognize an 8 bp site with a theoretical affinity of $4 \times 10^{10} M^{-1}$. The difference in affinity between the monomer X and the bis-X form is 200,000-fold. The number of 4 bp sites in the genome is approximately 1.2×10^7 versus the number of 8 bp sites in the genome which is approximately 5×10^4. Accordingly, there are 256-fold fewer 8 bp sites than 4 bp sites. Thus, the number of high affinity target sites is 256-fold fewer for the bis-X molecule than the number of low affinity target sites for the monomer X, with a 200,000-fold difference in affinity between the two types of sites.

Since the binding constant of a dimer is the product of the binding constants of the monomers, when monomers with higher initial binding constants are formed into dimers (or multimers) the differential effect is proportionately increased, creating a wider "window" of affinity versus the number of binding sites. The breadth of the window essentially reflects the margin of effective drug concentration compared to the relative toxicity.

There are two immediate ramifications of dimerization (or multimerization) of monomeric drugs with moderate toxicity and sequence preference. First, the concentration of drug needed is lowered because of the higher affinity, so that even relatively toxic molecules can be used as drugs. Second, since toxicity is

likely linked to the average number of drug molecules bound to the genome, as specificity is increased by increasing the length of the binding site, toxicity is decreased.

Given the information already available on sequence-preferential binding of DNA-binding drugs, it is likely that each drug presented to the screening assay will have (i) a number of high affinity binding sites (*e.g.*, 10 to 100-fold better affinity than the average site), (ii) a larger number of sites that are bound with moderate affinity (3 to 10-fold better affinity than average), (iii) the bulk of the binding sites having average affinity, and (iv) a number of sites having worse-than-average affinity. This range of binding affinities will likely resemble a bell-shaped curve. The shape of the curve will probably vary for each drug. To exemplify, assume that approximately five 4 bp sites will be high affinity binding sites, and twenty 4 bp sites will be moderately high affinity binding sites, then any given drug may recognize roughly 25, high or moderately high affinity binding sites. If 50 to 100 drugs are screened, this represents a "bank" of potentially 250-500 high affinity sites and 1000-2500 moderately high affinity sites. Thus, the probability of finding a number of high affinity drug binding sites that match medically significant target sites is good. Furthermore, heterodimeric drugs can be designed to match DNA target sites of 8 or more bp, lending specificity to the potential pharmaceuticals.

As discussed above, once the sequence preferences are known, the information may be used to design oligomeric molecules (homopolymers or heteropolymers) with substantially greater sequence specificity and substantially higher binding affinity. For example, if

a DNA-binding molecule, X, binds a 4 bp sequence 5'-ACGT-3'/5'-ACGT-3' with an equilibrium affinity constant of 2×10^5 M^{-1}, then the dimer of X, X_2, should bind the dimer of the sequence, 5'-ACGTACGT-3'/5'-ACGTACGT-3', with an equilibrium affinity constant of $(2 \times 10^5\ M^{-1})^2 = 4 \times 10^{10}\ M^{-2}$. The DNA-binding dimer molecule, X_2, recognizes an 8 bp sequence, conferring higher sequence specificity, with a binding affinity that is theoretically 200,000-fold higher than the DNA-binding monomer, X.

The same argument can be extended to trimer molecules: the trimer of X, X_3, would bind a 12 bp sequence, 5'-ACGTACGTACGT-3'/5'-ACGTACGTACGT-3', with a theoretical equilibrium affinity constant of $8 \times 10^{15} M^{-2}$.

DNA-binding polymers constructed using the above-mentioned approach may be homo- or hetero-polymers of the parent compounds or oligomeric compounds composed of mixed subunits of the parent compounds. Homopolymers are molecules constructed using two or more subunits of the same monomeric DNA-binding molecule. Heteropolymers are molecules constructed using two or more subunits of different monomeric DNA-binding molecules. Oligomeric compounds are constructed of mixed pieces of parent compounds and may be hetero- or homomeric.

For example, distamycin is a member of a family of non-intercalating minor groove DNA-binding oligopeptides that are composed of repeating units of N-methylpyrrole groups. Distamycin has 3 N-methylpyrrole groups. Examples of homopolymers would be bis-distamycin, the dimer of distamycin, a molecule containing 6 N-methylpyrrole groups or tris-distamycin, the trimer of distamycin, a molecule containing 9 N-methylpyrrole groups.

Daunomycin is a member of an entirely different class of DNA-binding molecules, the anthracycline antibiotics, that bind to DNA via intercalation. Heteropolymers are molecules composed of different types of DNA-binding subunits; for example, compounds composed of a distamycin molecule linked to a daunomycin molecule or a distamycin molecule linked to two daunomycin molecules. The term "oligomeric" is being used to describe molecules comprised of linked subunits each of which may be smaller than the parent compound.

An example of an homo-oligomeric compound would be a distamycin molecule linked to 1 or 2 additional N-methylpyrrole groups; the resulting molecule would not be as large as bis-distamycin, but would fundamentally be composed of the same component organic moieties that comprise the parent molecule. Examples of a hetero-oligomeric compounds would be daunomycin linked to one or two N-methylpyrrole groups.

The construction of these polymers will be directed by the information derived from the sequence preferences of the parent compounds tested in the assay. In one embodiment of the assay, a database of preferred sequences is constructed, providing a source of information about the 4 bp sequences that bind with relatively higher affinity to particular drugs that may be linked together to target any particular larger DNA sequence.

DNA-binding subunits can be chemically coupled to form heteropolymers or homopolymers. The subunits can be joined directly to each other, as in the family of distamycin molecules, or the subunits can be joined with a spacer molecule, such as carbon chains or peptide bonds. The coupling of subunits is dependent on the chemical nature of the subunits: appropriate coupling reactions can be determined for any two

subunit molecules from the chemical literature. The choice of subunits will be directed by the sequence to be targeted and the data accumulated through the methods discussed in Section VI.B of this application.

2. <u>Sequence-Specific DNA-Binding Molecules Identified in the Assay as Facilitators of Triplex Formation</u>.

Several types of nucleic acid base-containing polymers have been described that will form complexes with nucleic acids (for reviews, see Helene, C. and Toulme, J.-J.). One type of such a polymer forms a triple-stranded complex by the insertion of a third strand into the major groove of the DNA helix. Several types of base-recognition specific interactions of third strand oligonucleotide-type polymers have been observed. One type of specificity is due to Hoogsteen bonding (Hoogsteen). This specificity arises from recognition between pyrimidine oligonucleotides and double-stranded DNA by pairing thymine and adenine:thymine base pairs and protonated cytosine and guanine:cytosine base pairs (Griffin, *et al.*). Another type of specific interaction involves the use of purine oligonucleotides for triplex formation. In these triplexes, adenine pairs with adenine:thymine base pairs and guanine with guanine:cytosine (Cooney, *et al.*; Beal and Dervan) or thymine:adenine base paris (Griffen, L., and Dervan, P.B.).

Other motifs for triplex formation have been described, including the incorporation of nucleic acid analogs (eg, methylphosphonates, phosphorothioates; Miller, *et al.*), and the invention of backbones other than the phosphoribose backbones normally found in nucleic acids (Pitha, *et al.*; Summerton, *et al.*). In several cases, the formation of triplex has been

demonstrated to inhibit the binding of a DNA-binding protein (*e.g.*, Young, *et al.*; Maher, *et al.*) or the expression of a cellular protein (Cooney, et *al.*).

Furthermore, several experiments have been reported in which a small DNA-binding molecule has been covalently attached to polymer capable of forming a triplex structure: (i) an acridine:polypyrimidine molecule has been demonstrated to inhibit SV40 in CV-1 cells (Birg, *et al.*); (ii) cleavage at a single site in a yeast chromosome was achieved with an oligonucleotide:EDTA-Fe molecule (Strobel, *et al.*; Dervan); and (iii) a photoinducible endonuclease was created by similar strategy by attaching an ellipticine derivative to a homopyrimidine oligonucleotide (Perouault, *et al.*). Several other small intercalating agents coupled to oligonucleotides have been described (for review, see Montenay-Garestier).

One utility of the assay of the present invention is to identify the sequence-specificity of DNA-binding molecules for use in designing and synthesizing heteromeric therapeutics consisting of a DNA-binding polymer (*e.g.*, an oligonucleotide) attached to a sequence-preferential or sequence-specific DNA-binding molecule, yielding a heteropolymer. The attached small molecule may serve several functions.

First, if the molecule has increased affinity for a specific site (such as, a particular 4 base pair sequence) over all other sites of the same size, then the local concentration of the hetero-molecule, including the oligonucleotide, will be increased at those sites. The amount of heteropolymer, containing a sequence-specific moiety attached to one end, needed for treatment purposes is reduced compared to a heteropolymer that has a non-specific DNA-binding moiety attached. This reduction in treatment amount is directly

proportional to both the differential specificity and the relative affinities between the sequence-specific binder and the non-specific binder. For the simplest example, if a sequence-specific molecule with absolute specificity (*i.e.*, it binds only one sequence) had equal affinity for a specific 4 base-pair target site (1/256 possible combinations) as a non-specific molecule, then the amount of drug needed to exert the same effective concentration at that site could potentially be as much as 256-fold less for the specific and non-specific drugs. Accordingly, attaching a sequence-specific DNA-binding molecule to a polymer designed to form triplex structures allows increased localized concentrations.

A second utility of the assay of the present invention is to identify small molecules that cause conformational changes in the DNA when they bind. The formation of triplex DNA requires a shift from B form to A form DNA. This is not energetically favorable, necessitating the use of increased amounts of polymer for triplex formation to drive the conformational change. However, the insertion of a small DNA-binding molecule (such as, actinomycin D), which induces a conformational change in the DNA, reduces the amount of polymer needed to stabilize triplex formation.

Accordingly, one embodiment of the invention is to use the assay to test known DNA-binding molecules with all 256 possible four base pair test sequences to determine the relative binding affinity to all possible 4 bp sequences. Then, once the sequence preferences are known, the information may be used to design heteropolymeric molecules comprised of a small DNA-binding molecule and a macromolecule, such as a triplex-forming oligonucleotide, to obtain a DNA-binding molecule with enhanced binding characteristics.

The potential advantages of attaching a sequence-specific or sequence-preferential DNA-binding small molecule to a triplex forming molecule are to (i) target the triplex to a subset of specific DNA sequences and thereby (ii) anchor the triplex molecule in the vicinity of its target sequence and in doing so, (iii) increase the localized concentration of the triplex molecule, which allows (iv) lower concentrations of triplex to be used effectively. The presence of the small molecule may also facilitate localized perturbations in DNA structure, such as destabilizing the B form of DNA, which is unsuitable for triplex formation. Such destabalization may facilitate the formation of other structures, such a form DNA useful for triplex formation. The net effect would be to decrease the amount of triplex needed for efficacious results.

F. Other Applications.

The potential pharmaceutical applications for sequence-specific DNA-binding molecules are very broad, including antiviral, antifungal, antibacterial, antitumor agents, immunosuppressants, and cardiovascular drugs. Sequence-specific DNA-binding molecules can also be useful as molecular reagents as, for example, specific sequence probes.

As more DNA-binding molecules are detected, information about their DNA binding affinities, sequence recognition, and mechanisms of DNA-binding will be gathered, eventually facilitating the design and/or modification of new molecules with different or specialized activities.

Although the assay has been described in terms of the detection of sequence-specific DNA-binding molecules, the reverse assay could be achieved by adding

DNA in excess to protein to look for peptide sequence specific protein-binding inhibitors.

The following examples illustrate, but in no way are intended to limit, the present invention.

Materials and Methods

Synthetic oligonucleotides were prepared using commercially available automated oligonucleotide synthesizers. Alternatively, custom designed synthetic oligonucleotides may be purchased, for example, from Synthetic Genetics (San Diego, CA). Complementary strands were annealed to generate double-strand oligonucleotides.

Restriction enzymes were obtained from Boehringer Mannheim (Indianapolis IN) or New England Biolabs (Beverly MA) and were used as per the manufacturer's directions.

Distamycin A and Doxorubicin were obtained from Sigma (St. Louis, MO). Actinomycin D was obtained from Boehringer Mannheim or Sigma.

Standard cloning and molecular biology techniques are described in Ausubel, *et al.*, and Sambrook, *et al.*

Example 1

Preparation of the Oligonucleotide Containing the Screening Sequence

This example describes the preparation of (A) biotinylated/digoxigenin/radiolabeled, and (B) radiolabeled double-stranded oligonucleotides that contain the screening sequence and selected Test sequences.

A. Biotinylation.

The oligonucleotides were prepared as described above. The wild-type control sequence for the UL9

binding site, as obtained from HSV, is shown in Figure 4. The screening sequence, *i.e.* the UL9 binding sequence, is CGTTCGCACTT (SEQ ID NO:601) and is underlined in Figure 4. Typically, sequences 5′ and/or 3′ to the screening sequence were replaced by a selected Test sequence (Figure 5).

One example of the preparation of a site-specifically biotinylated oligonucleotide is outlined in Figure 4. An oligonucleotide primer complementary to the 3′ sequences of the screening sequence-containing oligonucleotide was synthesized. This oligonucleotide terminated at the residue corresponding to the C in position 9 of the screening sequence. The primer oligonucleotide was hybridized to the oligonucleotide containing the screening sequence. Biotin-11-dUTP (Bethesda Research Laboratories (BRL), Gaithersburg MD) and Klenow enzyme were added to this complex (Figure 4) and the resulting partially double-stranded biotinylated complexes were separated from the unincorporated nucleotides using either pre-prepared "G-25 SEPHADEX" spin columns (Pharmacia, Piscataway NJ) or "NENSORB" columns (New England Nuclear) as per manufacturer's instructions. The remaining single-strand region was converted to double-strands using DNA polymerase I Klenow fragment and dNTPs resulting in a fully double-stranded oligonucleotide. A second "G-25 SEPHADEX" column was used to purify the double-stranded oligonucleotide. Oligonucleotides were diluted or resuspended in 10 mM Tris-HCl, pH 7.5, 50 mM NaCl, and 1 mM EDTA and stored at -20°C. For radiolabelling the complexes, ^{32}P-alpha-dCTP (New England Nuclear, Wilmington, DE) replaced dCTP for the double-strand completion step.

Alternatively, the top strand, the primer, or the fully double-stranded oligonucleotide have been radiolabeled with γ-^{32}P-ATP and polynucleotide kinase

(NEB, Beverly, MA). Most of our preliminary studies have employed radiolabeled, double-stranded oligonucleotides. The oligonucleotides are prepared by radiolabeling the primer with T4 polynucleotide kinase and γ-^{32}P-ATP, annealing the "top" strand full length oligonucleotide, and "filling-in" with Klenow fragment and deoxynucleotide triphosphates. After phosphorylation and second strand synthesis, oligonucleotides are separated from buffer and unincorporated triphosphates using "G-25 SEPHADEX" preformed spin columns (IBI, New Haven, CT or Biorad, Richmond CA). This process is outlined in Figure 4. The reaction conditions for all of the above Klenow reactions were as follows: 10 mM Tris-HCl, pH 7.5, 10 mM $MgCl_2$, 50 mM NaCl, 1 mM dithioerythritol, 0.33-100 μM deoxytriphosphates, 2 units Klenow enzyme (Boehringer-Mannheim, Indianapolis IN). The Klenow reactions were incubated at 25°C for 15 minutes to 1 hour. The polynucleotide kinase reactions were incubated at 37°C for 30 minutes to 1 hour.

B. <u>End-Labeling with Digoxigenin</u>.

The biotinylated, radiolabelled oligonucleotides or radiolabeled oligonucleotides were isolated as above and resuspended in 0.2 M potassium cacodylate (pH=7.2), 4 mM $MgCl_2$, 1 mM 2-mercaptoethanol, and 0.5 mg/ml bovine serum albumin. To this reaction mixture digoxigenin-11-dUTP (an analog of dTTP, 2'-deoxyuridine-5'-triphosphate, coupled to digoxigenin via an 11-atom spacer arm, Boehringer Mannheim, Indianapolis IN) and terminal deoxynucleotidyl transferase (GIBCO BRL, Gaithersburg, MD) were added. The number of Dig-11-dUTP moieties incorporated using this method appeared to be less than 5 (probably only 1 or 2) as judged by electrophoretic mobility on polyacrylamide

gels of the treated fragment as compared to oligonucleotides of known length.

The biotinylated or non-biotinylated, digoxygenin-containing, radiolabelled oligonucleotides were isolated as above and resuspended in 10 mM Tris-HCl, 1 mM EDTA, 50 mM NaCl, pH 7.5 for use in the binding assays.

The above procedure can also be used to biotinylate the other strand by using an oligonucleotide containing the screening sequence complementary to the one shown in Figure 4 and a primer complementary to the 3' end of that molecule. To accomplish the biotinylation Biotin-7-dATP was substituted for Biotin-11-dUTP. Biotinylation was also accomplished by chemical synthetic methods: for example, an activated nucleotide is incorporated into the oligonucleotide and the active group is subsequently reacted with NHS-LC-Biotin (Pierce). Other biotin derivatives can also be used.

C. <u>Radiolabelling the Oligonucleotides</u>.

Generally, oligonucleotides were radiolabelled with gamma-^{32}P-ATP or alpha-^{32}P-deoxynucleotide triphosphates and T4 polynucleotide kinase or the Klenow fragment of DNA polymerase, respectively. Labelling reactions were performed in the buffers and by the methods recommended by the manufacturers (New England Biolabs, Beverly MA; Bethesda Research Laboratories, Gaithersburg MD; or Boehringer/Mannheim, Indianapolis IN). Oligonucleotides were separated from buffer and unincorporated triphosphates using "G-25 SEPHADEX" preformed spin columns (IBI, New Haven, CT; or Biorad, Richmond, CA) or "NENSORB" preformed columns (New England Nuclear, Wilmington, DE) as per the manufacturers instructions.

There are several reasons to enzymatically synthesize the second strand. The two main reasons are that by using an excess of primer, second strand synthesis can be driven to near completion so that nearly all top strands are annealed to bottom strands, which prevents the top strand single strands from folding back and creating additional and unrelated double-stranded structures, and secondly, since all of the oligonucleotides are primed with a common primer, the primer can bear the end-label so that all of the oligonucleotides will be labeled to exactly the same specific activity.

Example 2

Preparation of the UL9 Protein

A. Cloning of the UL9 Protein-Coding Sequences into pAC373.

To express full length UL9 protein a baculovirus expression system has been used. The sequence of the UL9 coding region of Herpes Simplex Virus has been disclosed by McGeoch *et al.* and is available as an EMBL nucleic acid sequence. The recombinant baculovirus AcNPV/UL9A, which contained the UL9 protein-coding sequence, was obtained from Mark Challberg (National Institutes of Health, Bethesda MD). The construction of this vector has been previously described (Olivo, *et al.* (1988, 1989)). Briefly, the *NarI/EcoRV* fragment was derived from pMC160 (Wu, *et al.*). Blunt-ends were generated on this fragment by using all four dNTPs and the Klenow fragment of DNA polymerase I (Boehringer Mannheim, Indianapolis IN) to fill in the terminal overhangs. The resulting fragment was blunt-end ligated into the unique *BamHI* site of the baculoviral vector pAC3T3 (Summers, *et al.*).

B. Cloning of the UL9 Sequence in pVL1393.

The UL9 protein-coding region was cloned into a second baculovirus vector, pVL1393 (Luckow, *et al.*). The 3077 bp *NarI/EcoRV* fragment containing the UL9 gene was excised from vector pEcoD (obtained from Dr. Bing Lan Rong, Eye Research Institute, Boston, MA): the plasmid pEcoD contains a 16.2 kb EcoRI fragment derived from HSV-I that bears the UL9 gene (Goldin, *et al.*). Blunt-ends were generated on the UL9-containing fragment as described above. *EcoRI* linkers (10 mer) were blunt-end ligated (Ausubel, *et al.*; Sambrook, *et al.*) to the blunt-ended *NarI/EcoRV* fragment.

The vector pVL1393 (Luckow, *et al.*) was digested with *EcoRI* and the linearized vector isolated. This vector contains 35 nucleotides of the 5′ end of the coding region of the polyhedron gene upstream of the polylinker cloning site. The polyhedron gene ATG has been mutated to ATT to prevent translational initiation in recombinant clones that do not contain a coding sequence with a functional ATG. The *EcoRI*/UL9 fragment was ligated into the linearized vector, the ligation mixture transformed into *E. coli* and ampicillin resistant clones selected. Plasmids recovered from the clones were analyzed by restriction digestion and plasmids carrying the insert with the amino terminal UL9 protein-coding sequences oriented to the 5′ end of the polyhedron gene were selected. This plasmid was designated pVL1393/UL9 (Figure 7).

pVL1393/UL9 was cotransfected with wild-type baculoviral DNA (AcMNPV; Summers, *et al.*) into SF9 (*Spodoptera frugiperda*) cells (Summers, *et al.*). Recombinant baculovirus-infected Sf9 cells were identified and clonally purified (Summers, *et al.*).

C. Expression of the UL9 Protein.

Clonal isolates of recombinant baculovirus infected Sf9 cells were grown in Grace's medium as described by Summers, *et al.* The cells were scraped from tissue culture plates and collected by centrifugation (2,000 rpm, for 5 minutes, 4°C). The cells were then washed once with phosphate buffered saline (PBS) (Maniatis, *et al.*). Cell pellets were frozen at -70°C. For lysis the cells were resuspended in 1.5 volumes 20 mM HEPES, pH 7.5, 10% glycerol, 1.7 M NaCl, 0.5 mM EDTA, 1 mM dithiothreitol (DTT), and 0.5 mM phenyl methyl sulfonyl fluoride (PMSF). Cell lysates were cleared by ultracentrifugation (Beckman table top ultracentrifuge, TLS 55 rotor, 34 krpm, 1 hr, 4°C). The supernatant was dialyzed overnight at 4°C against 2 liters dialysis buffer (20 mM HEPES, pH 7.5, 10% glycerol, 50 mM NaCl, 0.5 mM EDTA, 1 mM dtt, and 0.1 mM PMSF).

These partially purified extracts were prepared and used in DNA:protein binding experiments. If necessary extracts were concentrated using a "CENTRICON 30" filtration device (Amicon, Danvers MA).

D. Cloning the Truncated UL9 Protein.

The sequence encoding the C-terminal third of UL9 and the 3' flanking sequences, an approximately 1.2 kb fragment, was subcloned into the bacterial expression vector, pGEX-2T (Figure 6). The pGEX-2T is a modification of the pGEX-1 vector of Smith, *et al.* which involved the insertion of a thrombin cleavage sequence in-frame with the glutathione-S-transferase protein (gst).

A 1,194 bp *BamHI/EcoRV* fragment of pEcoD was isolated that contained a 951 bp region encoding the C-

terminal 317 amino acids of UL9 and 243 bp of the 3' untranslated region.

This *BamHI/EcoRV* UL9 carboxy-terminal (UL9-COOH) containing fragment was blunt-ended and *EcoRI* linkers added as described above. The *EcoRI* linkers were designed to allow in-frame fusion of the UL9 protein-coding sequence to the gst-thrombin coding sequences. The linkered fragment was isolated and digested with *EcoRI*. The pGEX-2T vector was digested with *EcoRI*, treated with Calf Intestinal Alkaline Phosphatase (CIP) and the linear vector isolated. The *EcoRI* linkered UL9-COOH fragment was ligated to the linear vector (Figure 6). The ligation mixture was transformed into *E. coli* and ampicillin resistant colonies were selected. Plasmids were isolated from the ampicillin resistant colonies and analyzed by restriction enzyme digestion. A plasmid which generated a gst/thrombin/-UL9-COOH in frame fusion was identified (Figure 6) and designated pGEX-2T/UL9-COOH.

E. <u>Expression of the Truncated UL9 Protein</u>.

E. coli strain JM109 was transformed with pGEX-2T/C-UL9-COOH and was grown at 37°C to saturation density overnight. The overnight culture was diluted 1:10 with LB medium containing ampicillin and grown from one hour at 30°C. IPTG (isopropyllthio-β-galactoside) (GIBCO-BRL) was added to a final concentration of 0.1 mM and the incubation was continued for 2-5 hours. Bacterial cells containing the plasmid were subjected to the temperature shift and IPTG conditions, which induced transcription from the *tac* promoter.

Cells were harvested by centrifugation and resuspended in 1/100 culture volume of MTPBS (150 mM NaCl, 16 mM Na_2HPO_4, 4 mM NaH_2PO_4). Cells were lysed by

sonication and lysates cleared of cellular debris by centrifugation.

The fusion protein was purified over a glutathione agarose affinity column as described in detail by Smith, *et al.* The fusion protein was eluted from the affinity column with reduced glutathione, dialyzed against UL9 dialysis buffer (20 mM HEPES pH 7.5, 50 mM NaCl, 0.5 mM EDTA, 1 mM DTT, 0.1 mM PMSF) and cleaved with thrombin (2 ng/ug of fusion protein).

An aliquot of the supernatant obtained from IPTG-induced cultures of pGEX-2T/C-UL9-COOH-containing cells and an aliquot of the affinity-purified, thrombin-cleaved protein were analyzed by SDS-polyacrylamide gel electrophoresis. The result of this analysis is shown in Figure 8. The 63 kilodalton GST/C-UL9 fusion protein is the largest band in the lane marked GST-UL9 (lane 2). The first lane contains protein size standards. The UL9-COOH protein band (lane GST-UL9 + Thrombin, Figure 8, lane 3) is the band located between 30 and 46 kD: the glutathione transferase protein is located just below the 30 kD size standard. In a separate experiment a similar analysis was performed using the uninduced culture: it showed no protein corresponding in size to the fusion protein.

Extracts are dialyzed before use. Also, if necessary, the extracts can be concentrated typically by filtration using a "CENTRICON 30" filter.

Example 3

Binding Assays

A. Band Shift Gels.

DNA:protein binding reactions containing both labelled complexes and free DNA were separated electrophoretically on 4-10% polyacrylamide/Tris-Borate-EDTA (TBE) gels (Fried, *et al.*; Garner, *et al.*). The gels

were then fixed, dried, and exposed to X-ray film. The autoradiograms of the gels were examined for band shift patterns.

B. Filter Binding Assays.

A second method used particularly in determining the half-lives for oligonucleotide:protein complexes is filter binding (Woodbury, *et al.*). Nitrocellulose disks (Schleicher and Schuell, BA85 filters) that have been soaked in binding buffer (see below) were placed on a vacuum filter apparatus. DNA:protein binding reactions (see below; typically 15-30 μl) are diluted to 0.5 ml with binding buffer (this dilutes the concentration of components without dissociating complexes) and applied to the discs with vacuum applied. Under low salt conditions the DNA:protein complex sticks to the filter while free DNA passes through. The discs are placed in scintillation counting fluid (New England Nuclear), and the cpm determined using a scintillation counter.

This technique has been adapted to 96-well and 72-slot nitrocellulose filtration plates (Schleicher and Schuell) using the above protocol except (i) the reaction dilution and wash volumes are reduced, and (ii) the flow rate through the filter is controlled by adjusting the vacuum pressure. This method greatly facilitates the number of assay samples that can be analyzed. Using radioactive oligonucleotides, the samples are applied to nitrocellulose filters, the filters are exposed to x-ray film, then analyzed using a Molecular Dynamics scanning densitometer. This system transfers data directly into analytical software programs (*e.g.*, Excel) for analysis and graphic display.

Example 4

Functional UL9 Binding Assay

A. Functional DNA-Binding Activity Assay.

Purified protein was tested for functional activity using band-shift assays. Radiolabelled oligonucleotides (prepared as in Example 1B) that contain the 11 bp recognition sequence were mixed with the UL9 protein in binding buffer (optimized reaction conditions: 0.1 ng ^{32}P-DNA, 1 ul UL9 extract, 20 mM HEPES, pH 7.2, 50 mM KCl, and 1 mM DTT). The reactions were incubated at room temperature for 10 minutes (binding occurs in less than 2 minutes), then separated electrophoretically on 4-10% non-denaturing polyacrylamide gels. UL9-specific binding to the oligonucleotide is indicated by a shift in mobility of the oligonucleotide on the gel in the presence of the UL9 protein but not in its absence. Bacterial extracts containing (+) or without (-) UL9 protein and affinity purified UL9 protein were tested in the assay. Only bacterial extracts containing UL9 or affinity purified UL9 protein generate the gel band-shift indicating protein binding.

The degree of extract that needed to be added to the reaction mix, in order to obtain UL9 protein excess relative to the oligonucleotide, was empirically determined for each protein preparation/extract. Aliquots of the preparation were added to the reaction mix and treated as above. The quantity of extract at which the majority of the labelled oligonucleotide appears in the DNA:protein complex was evaluated by band-shift or filter binding assays. The assay is most sensitive under conditions in which the minimum amount of protein is added to bind most of the DNA. Excess protein decreases the sensitivity of the assay with respect to the ability of inhibitors to compete with

the protein for oligonucleotide binding, except when protein concentrations are so high that non-specific protein/DNA binding is provoked.

B. Rate of Dissociation.

The rate of dissociation is determined using a competition assay. An oligonucleotide having the sequence presented in Figure 4, which contained the binding site for UL9 (SEQ ID NO:614), was radiolabelled with ^{32}P-ATP and polynucleotide kinase (Bethesda Research Laboratories). The competitor DNA was a 17 base pair oligonucleotide (SEQ ID NO:616) containing the binding site for UL9.

In the competition assays, the binding reactions (Example 4A) were assembled with each of the oligonucleotides and placed on ice. Unlabelled oligonucleotide (1 μg) was added 1, 2, 4, 6, or 21 hours before loading the reaction on an 8% polyacrylamide gel (run in TBE buffer (Maniatis, *et al.*)) to separate the reaction components. The dissociation rates, under these conditions, for the truncated UL9 (UL9-COOH) and the full length UL9 is approximately 4 hours at 4°C. In addition, random oligonucleotides (a 10,000-fold excess) that did not contain the UL9 binding sequence and sheared herring sperm DNA (a 100,000-fold excess) were tested: neither of these control DNAs competed for binding with the oligonucleotide containing the UL9 binding site.

C. Optimization of the UL9 Binding Assay.

1. Truncated UL9 from the Bacterial Expression System.

The effects of the following components on the binding and dissociation rates of UL9-COOH with its cognate binding site have been tested and optimized:

buffering conditions (including the pH, type of buffer, and concentration of buffer); the type and concentration of monovalent cation; the presence of divalent cations and heavy metals; temperature; various polyvalent cations at different concentrations; and different redox reagents at different concentrations. The effect of a given component was evaluated starting with the reaction conditions given above and based on the dissociation reactions described in Example 4B.

The optimized conditions used for the binding of UL9-COOH contained in bacterial extracts (Example 2E) to oligonucleotides containing the HSV ori sequence (SEQ ID NO:601) were as follows: 20 mM HEPES, pH 7.2, 50 mM KCl, 1 mM DTT, 0.005 - 0.1 ng radiolabeled (specific activity, approximately 10^8 cpm/μg) or digoxiginated, biotinylated oligonucleotide probe, and 5-10 μg crude UL9-COOH protein preparation (1 mM EDTA is optional in the reaction mix). Under optimized conditions, UL9-COOH binds very rapidly and has a dissociation rate of about 4 hours at 4°C with non-biotinylated oligonucleotide and 5-10 minutes with biotinylated oligonucleotides. The dissociation rate of UL9-COOH changes markedly under different physical conditions. Typically, the activity of a UL9 protein preparation was assessed using the gel band-shift assay and related to the total protein content of the extract as a method of standardization. The addition of herring sperm DNA depended on the purity of UL9 used in the experiment Binding assays were incubated at 25°C for 5-30 minutes.

2. Full Length UL9 Protein from the Baculovirus System.

The binding reaction conditions for the full length baculovirus-produced UL9 polypeptide have also

been optimized. The optimal conditions for the current assay were determined to be as follows: 20 mM Hepes; 100 mM NaCl; 0.5 mM dithiothreitol; 1 mM EDTA; 5% glycerol; from 0 to 10^4-fold excess of sheared herring sperm DNA; 0.005 - 0.1 ng radiolabeled (specific activity, approximately 10^8 cpm/μg) or digoxiginated, biotinylated oligonucleotide probe, and 5-10 μg crude UL9 protein preparation. The full length protein also binds well under the optimized conditions established for the truncated UL9-COOH protein.

Example 5

The Effect of Test Sequence Variation on the Half-Life of the UL9 DNA:Protein Complex

The oligonucleotides shown in Figure 5 were radiolabelled as described above. The competition assays were performed as described in Example 4B using UL9-COOH. Radiolabelled oligonucleotides were mixed with the UL9-COOH protein in binding buffer (typical reaction: 0.1 ng oligonucleotide ^{32}P-DNA, 1 μl UL9-COOH extract, 20 mM HEPES, pH 7.2, 50 mM KCl, 1 mM EDTA, and 1 mM DTT). The reactions were incubated at room temperature for 10 minutes. A zero time point sample was then taken and loaded onto an 8% polyacrylamide gel (run use TBE). One μg of the unlabelled 17 bp competitive DNA oligonucleotide (SEQ ID NO:616) (Example 4B) was added at 5, 10, 15, 20, or 60 minutes before loading the reaction sample on the gel. The results of this analysis are shown in Figure 9: the screening sequences that flank the UL9 binding site (SEQ ID NO:605-SEQ ID NO:613) are very dissimilar but have little effect on the off-rate of UL9. Accordingly, these results show that the UL9 DNA binding protein is effective to bind to a screening sequence in duplex DNA with a binding affinity that is substantially

independent of test sequences placed adjacent the screening sequence. Filter binding experiments gave the same result.

Example 6

The Effect of Actinomycin D, Distamycin A, and Doxorubicin on UL9 Binding to the screening Sequence is Dependent on the Specific Test Sequence

Different oligonucleotides, each of which contained the screening sequence (SEQ ID NO:601) flanked on the 5′ and 3′ sides by a test sequence (SEQ ID NO:605 to SEQ ID NO:613), were evaluated for the effects of distamycin A, actinomycin D, and doxorubicin on UL9-COOH binding.

Binding assays were performed as described in Example 5. The oligonucleotides used in the assays are shown in Figure 5. The assay mixture was allowed to pre-equilibrate for 15 minutes at room temperature prior to the addition of drug.

A concentrated solution of Distamycin A was prepared in dH_2O and was added to the binding reactions at the following concentrations: 0, 1 μM, 4 μM, 16 μM, and 40 μM. The drug was added and incubated at room temperature for 1 hour. The reaction mixtures were then loaded on an 8% polyacrylamide gel (Example 5) and the components separated electrophoretically. Autoradiographs of these gels are shown in Figure 10A. The test sequences tested were as follows: UL9 polyT, SEQ ID NO:609; UL9 CCCG, SEQ ID NO:605; UL9 GGGC, SEQ ID NO:606; UL9 polyA, SEQ ID NO:608; and UL9 ATAT, SEQ ID NO:607. These results demonstrate that Distamycin A preferentially disrupts binding to UL9 polyT, UL9 polyA and UL9 ATAT.

A concentrated solution of Actinomycin D was prepared in dH_2O and was added to the binding reactions

at the following concentrations: 0 μM and 50 μM. The drug was added and incubated at room temperature for 1 hour. Equal volumes of dH_2O were added to the control samples. The reaction mixtures were then loaded on an 8% polyacrylamide gel (Example 5) and the components separated electrophoretically. Autoradiographs of these gels are shown in Figure 10B. In addition to the test sequences tested above with Distamycin A, the following test sequences were also tested with Actinomycin D: ATori1, SEQ ID NO:611; oriEco2, SEQ ID NO:612, and oriEco3, SEQ ID NO:613. These results demonstrate that actinomycin D preferentially disrupts the binding of UL9 to the oligonucleotides UL9 CCCG and UL9 GGGC.

A concentrated solution of Doxorubicin was prepared in dH_2O and was added to the binding reactions at the following concentrations: 0 μM, 15 μM and 35 μM. The drug was added and incubated at room temperature for 1 hour. Equal volumes of dH_2O were added to the control samples. The reaction mixtures were then loaded on an 8% polyacrylamide gel (Example 5) and the components separated electrophoretically. Autoradiographs of these gels are shown in Figure 10C. The same test sequences were tested as for Actinomycin D. These results demonstrate that Doxorubicin preferentially disrupts the binding of UL9 to the oligonucleotides UL9polyT, UL9 GGGC, oriEco2, and oriEco3. Doxorubicin appears to particularly disrupt the UL9:screening sequence interaction when the test sequence oriEco3 is used. The sequences of the test sequences for oriEco2 and oriEco3 differ by only one base: an additional T residue inserted at position 12, compare SEQ ID NO:612 and SEQ ID NO:613.

Example 7

Use of the Biotin/Streptavidin Reporter System

A. The Capture of Protein-Free DNA.

Several methods have been employed to sequester unbound DNA from DNA:protein complexes.

1. Magnetic Beads.

Streptavidin-conjugated superparamagnetic polystyrene beads (Dynabeads M-280 Streptavidin, Dynal AS, 6-7x10^8 beads/ml) are washed in binding buffer then used to capture biotinylated oligonucleotides (Example 1). The beads are added to a 15 ul binding reaction mixture containing binding buffer and biotinylated oligonucleotide. The beads/oligonucleotide mixture is incubated for varying lengths of time with the binding mixture to determine the incubation period to maximize capture of protein-free biotinylated oligonucleotides. After capture of the biotinylated oligonucleotide, the beads can be retrieved by placing the reaction tubes in a magnetic rack (96-well plate magnets are available from Dynal). The beads are then washed.

2. Agarose Beads.

Biotinylated agarose beads (immobilized D-biotin, Pierce, Rockford, IL) are bound to avidin by treating the beads with 50 µg/µl avidin in binding buffer overnight at 4°C. The beads are washed in binding buffer and used to capture biotinylated DNA. The beads are mixed with binding mixtures to capture biotinylated DNA. The beads are removed by centrifugation or by collection on a non-binding filter disc.

For either of the above methods, quantification of the presence of the oligonucleotide depends on the method of labelling the oligonucleotide. If the oligonucleotide is radioactively labelled: (i) the beads and supernatant can be loaded onto polyacrylamide gels

to separate DNA:protein complexes from the bead:DNA complexes by electrophoresis, and autoradiography performed; (ii) the beads can be placed in scintillation fluid and counted in a scintillation counter. Alternatively, presence of the oligonucleotide can be determined using a chemiluminescent or colorimetric detection system.

B. Detection of Protein-Free DNA.

The DNA is end-labelled with digoxigenin-11-dUTP (Example 1). The antigenic digoxigenin moiety is recognized by an antibody-enzyme conjugate, anti-digoxigenin-alkaline phosphatase (Boehringer Mannheim Indianapolis IN). The DNA/antibody-enzyme conjugate is then exposed to the substrate of choice. The presence of dig-dUTP does not alter the ability of protein to bind the DNA or the ability of streptavidin to bind biotin.

1. Chemiluminescent Detection.

Digoxigenin-labelled oligonucleotides are detected using the chemiluminescent detection system "SOUTHERN LIGHTS" developed by Tropix, Inc. (Bedford, MA). Use of this detection system is illustrated in Figures 11A and 11B. The technique can be applied to detect DNA that has been captured on either beads or filters.

Biotinylated oligonucleotides, which have terminal digoxygenin-containing residues (Example 1), are captured on magnetic (Figure 11A) or agarose beads (Figure 11B) as described above. The beads are isolated and treated to block non-specific binding by incubation with I-Light blocking buffer (Tropix) for 30 minutes at room temperature. The presence of oligonucleotides is detected using alkaline phosphatase-

conjugated antibodies to digoxygenin. Anti-digoxigenin-alkaline phosphatase (anti-dig-AP, 1:5000 dilution of 0.75 units/ul, Boehringer Mannheim) is incubated with the sample for 30 minutes, decanted, and the sample washed with 100 mM Tris-HCl, pH 7.5, 150 mM NaCl. The sample is pre-equilibrated with 2 washes of 50 mM sodium bicarbonate, pH 9.5, 1 M $MgCl_2$, then incubated in the same buffer containing 0.25 mM 3-(2'-spiroadamantane)-4-methoxy-4-(3'-phosphoryloxy) phenyl-1,2-dioxetane disodium salt (AMPPD) for 5 minutes at room temperature. AMPPD was developed (Tropix Inc.) as a chemiluminescent substrate for alkaline phosphatase. Upon dephosphorylation of AMPPD the resulting compound decomposes, releasing a prolonged, steady emission of light at 477 nm.

Excess liquid is removed from filters and the emission of light occurring as a result of the dephosphorylation of AMPPD by alkaline phosphatase can be measured by exposure to x-ray film or by detection in a luminometer.

In solution, the bead-DNA-anti-dig-AP is resuspended in "SOUTHERN LIGHT" assay buffer and AMPPD and measured directly in a luminometer. Large scale screening assays are performed using a 96-well plate-reading luminometer (Dynatech Laboratories, Chantilly, VA). Subpicogram quantities of DNA (10^2 to 10^3 attomoles (an attomole is 10^{-18} moles)) can be detected using the Tropix system in conjunction with the plate-reading luminometer.

2. Colorimetric Detection.

Standard alkaline phosphatase colorimetric substrates are also suitable for the above detection reactions. Typically substrates include 4-nitrophenyl phosphate (Boehringer Mannheim). Results of colorime-

tric assays can be evaluated in multiwell plates (as above) using a plate-reading spectrophotometer (Molecular Devices, Menlo Park CA). The use of the light emission system is more sensitive than the colorimetric systems.

Example 8

Labelling Test Oligonucleotides to Equivalent Specific Activities

The top strands of 256 oligonucleotides, containing all possible 4 bp sequences in the test sites flanking the UL9 recognition site, were synthesized. The oligonucleotides were composed of identical sequences except for the 4 bp sites flanking either side of the UL9 recognition sequence (SEQ ID No:601). The oligonucleotides had the general sequence presented in Figure 14B (SEQ ID NO:617), where XXXX is the test sequence and N = A,G,C, or T. A 12 bp primer sequence, which is the complementary sequence to the 3'-end of the test oligonucleotide, was also synthesized: the primer was designated the HSV primer and is presented as SEQ ID NO:618.

The HSV primer was used to prime second strand synthesis and to facilitate labeling the oligonucleotides to the same specific activity. Oligonucleotide labelling was accomplished by labeling the 5' end of the HSV primer and then using the same primer to prime second strand synthesis of all 256 test oligonucleotides. The 5' end of the primer can be labeled with radioisotopes such as ^{32}P, ^{33}P, or ^{35}S, or with non-radioactive detection systems such as digoxygenin or biotin as discussed in the Capture/Detection section.

Radioactive-labeling of the primer with ^{32}P is accomplished by the enzymatic transfer of a radioactive phosphate from γ-^{32}P-ATP to the 5' end of the primer

oligonucleotide using T4 polynucleotide kinase (Ausubel, *et al.*). For labeling 256 oligonucleotides, approximately 60 μg HSV primer was labeled as follows. The oligonucleotide was incubated for 1 hour at 37°C with 125 μl γ-^{32}P-ATP (20 mCi total, 7000 Ci/mmol) and 600 units of T4 polynucleotide kinase in a 3 ml reaction volume containing 50 mM Tris-HCL, pH 7.5, 10 mM $MgCl_2$, 10 mM spermidine, and 1.5 mM dithiothreitol (freshly prepared). To stop the reaction, EDTA was added to a final concentration of 20 mM. Unincorporated nucleotides were removed using "G-25 SEPHADEX" chromatography in 10 mM Tris-HCL, pH 7.5, 50 mM NaCl, and 1 mM EDTA (TE+50).

The radioactive primer was individually annealed to the top strand of each of the 256 test oligonucleotides. The bottom strand is synthesized using deoxyribonucleotides and Klenow fragment or T4 polymerase (Ausubel, *et al.*). The annealing mixture typically contained 200 ng HSV primer mixed with 1 μg top strand in 20 mM Tris-HCL, pH 7.5, 1 mM spermidine, and 0.1 mM EDTA (35 μl reaction volume). The primer was annealed to the top strand by incubating the sample for 2 minutes at 70°C, then placing the sample at room temperature or on ice. To the annealing mixture, 4.5 μl 10x Klenow buffer (10X = 200 mM Tris-HCL, 500 mM NaCl, 50 mM $MgCl_2$, 10 mM dithiothreitol), 5 μl 0.5 mM each dNTP (dATP, dCTP, dGTP, dTTP), and 1 μl Klenow fragment were added. This reaction mixture was incubated 30-60 minutes at room temperature (or up to 37°C).

The volume of the reaction mixture was increased by adding 75 μl a solution of 10 mM Tris-HCl, pH 7.5, 50 mM NaCl, and 10 mM EDTA. The reaction mixture was applied to a 1 ml "G-25 SEPHADEX" (in TE+50) spin column. The spin columns were prepared by plugging 1cc

tuberculin syringes with silanized glass wool and adding a slurry of "G-25 SEPHADEX." The columns were prespun at 2000 rpm in a tabletop centrifuge for 4 minutes. The samples (reaction mixtures) were passed through the column by centrifugation (2000 rpm, 4 minutes at room temperature) to remove unincorporated deoxyribonucleotides. The incorporation of ^{32}P was measured by placing a small volume of the sample in scintillation fluor and determining the disintegrations per minute (dpms) in a scintillation counter.

The radiolabeled double-stranded oligonucleotides were then diluted to the same specific activity (equal dpms per volume). Typically, a concentration of 0.1 to 1 ng/μl oligonucleotide was used in the assay.

The same procedure can be used for second strand synthesis and labeling to equal specific activity regardless of the type of label on the HSV primer.

Example 9

An Arrayed Sample Format

Screening large numbers of test molecules or test sequences is most easily accomplished in an arrayed sample format, for example, a 96-well plate format. Such formats are readily amenable to automation using robotics systems. Several different types of disposable plastic plates are available for use in screening assays including the following: polyvinyl chloride (PVC), polypropylene (PP), polyethylene (PE), and polystyrene (PS) plates. Plates, or any testing vehicle in which the assay is performed, are tested for protein and DNA adsorption and coated with a blocking reagent if necessary.

One method for testing protein or DNA adsorption to plates is to place assay mixtures in the wells of the plates for varying lengths of time. Samples are

then removed from the wells and a nitrocellulose dot blot capture system (Ausubel, *et al.*; Schleicher and Schuell) is used to measure the amount of DNA:protein complex remaining in the mixture over time.

When radiolabeled oligonucleotides are used for the test, signal can be measured using autoradiography and a scanning laser densitometer. A decrease in the amount of DNA:protein complex in the absence of competitor molecules is indicative of plate adsorption. If plate adsorption occurs, the plates are coated with a blocking agent prior to use in the assay.

None of the plates listed above showed marked adsorption at a 30 minute time point under the conditions of the assay. However, most plates, regardless of brand, showed significant adsorption at times greater than 2 hours.

Coating the plates with a blocking agent decreases variability in the assay. Several types of blocking reagents typically used to block the adsorption of macromolecules to plastic are known, primarily from immunoscreening procedures. For example, plates may be blocked with either 1% bovine serum albumin (BSA) in phosphate-buffered saline (PBS), or 0.1% gelatin, 0.05% "TWEEN29" in PBS.

To test for the effectiveness of using such blocking reagents, the plates were treated with the above reagents for 1 hour at room temperature, then washed three times with 0.05% "TWEEN20" in PBS and once with the assay buffer. Assay reaction mixtures were aliquoted to the plates and tested as described above using dot blot capture assays. Both of the blocking reagents (BSA or gelatin) were effective in blocking DNA and protein binding -- except when polypropylene plates were used. Based on these experiments, PVC

plates blocked with BSA were determined to work well in the assay of the present invention.

Plates were tested for inter- and intra-plate variability by aliquoting duplicate samples to all 96-wells of several plates, and determining the amount of DNA:protein complex recovered using the dot blot/nitrocellulose system. The coefficient of variation [%CV = (the standard deviation/mean)*100] was calculated for intra-plate variability (*i.e.*, between samples on the same plate) and inter-plate variability (*i.e.*, between plates). Blocked PVC plates showed an intra-plate %CV of 5-20%; inter-plate variability was about 8%.

Example 10

Sequence Selectivity and Relative Binding Affinity for Distamycin

Using the assay method of the present invention, distamycin was tested for sequence selectivity and relative binding affinity to 256 different 4 bp sequences.

A. The Assay Mixture.

Water, buffer and UL9 were mixed on ice and aliquoted to the wells of a 96-well plate. The addition of water/UL9/buffer mix was accomplished with an 8-channel repipettor, which holds a relatively large volume and allowed rapid, accurate pipetting to all 96 wells of a master experimental plate.

Radiolabeled double-stranded oligonucleotides were aliquoted from 96-well master stock plates (containing the array of all 256 oligonucleotides diluted to the same specific activity) to the wells of the master experimental plates.

Master assay mixtures in the master experimental plates were thoroughly mixed by pipetting up and down. The mixtures were aliquoted to the test plates. Each test plate typically included one sample as a control (no test molecules added) and as many test samples as were needed for different test molecules or test molecule concentrations. There were 3 master oligonucleotide stock plates, containing the array of 256 oligonucleotides. Accordingly, an experiment testing distamycin at different concentrations would require 256 control assays (one for each oligonucleotide) and 256 assays at each of the drug concentrations to be tested.

The following assay mixture was used for testing distamycin in the assay of the present invention: 1.5 nM radiolabeled DNA and 12.8 nM UL9-COOH protein (prepared as described above in the UL9 binding buffer; 20 mM Hepes, pH 7.2, 50 mM KCl, and 1 mM dithiothreitol). The concentration of the components in the assay mixture can be varied as described above in the Detailed Description.

Assay mixtures containing both UL9 and DNA were incubated at room temperature for at least 10 minutes to allow the DNA:protein complexes to form and for the system to come to equilibrium. At time = 0, the assay was begun by adding water (control samples) or distamycin (5-15 μM, test samples) to the assay mixtures using a 12-channel micropipettor. After incubation with drug for 5-120 minutes, samples were taken and applied to nitrocellulose on a 96-well dot blot apparatus (Schleicher and Schuell). The samples were held at 4°C.

Tests were performed in duplicate. Typically, one set of 256 test oligonucleotides was scrambled with respect to location on the 96-well plate to eliminat any effects of plate location.

B. The Capture/Detection System.

A 96-well dot blot apparatus was used to capture the DNA:protein complexes on a nitrocellulose filter. The filters used in the dot blot apparatus were pretreated as follows. The nitrocellulose filter was pre-wetted with water and soaked in UL9 binding buffer. The filter was then placed on 1 to 3 pieces of 3MM filter paper, which were also presoaked in UL9 binding buffer. All filters were chilled to 4°C prior to placement in the apparatus.

Prior to the application of the assay sample to the wells of the dot-blot apparatus, the wells were filled with 375 μl of UL9 binding buffer. Typically, 5-50 μl of sample (usually 10-15 μl) were pipetted into the wells containing binding buffer and a vacuum applied to the system to pull the sample through the nitrocellulose. Unbound DNA passes through the nitrocellulose, protein-bound DNA sticks to the nitrocellulose. The filters were dried and exposed to X-ray film to generate autoradiographs.

C. Quantitation of Data.

The autoradiographs of the nitrocellulose filters were analyzed with a Molecular Dynamics (Sunnyvale, CA) scanning laser densitometer using an ImageQuant software package (Molecular Dynamics). Using this software, a 96-well grid was placed on the image of the autoradiograph and the densitometer calculated the "volume" of each dot ("volume" is equivalent to the density of each pixel in the grid square multiplied by the area of the grid square). The program automatically subtracts background. The background was determined by either the background of a line or object drawn outside the grid or by using the gridlines as background for each individual dot.

The data is exported to a spreadsheet program, such as "EXCEL" (Microsoft Corporation, Redmond, WA) for further analysis.

D. Analysis of Data.

The data generate from the densitometry analysis was analyzed using the spreadsheet program "EXCEL."

For each test oligonucleotide, at each drug concentration and/or each time point, a raw % score was calculated. The raw % score (r%) can be described as

$$r\% = (T/C) \times 100$$

where T was the densitometry volume of the test sample and C was the densitometry volume of the control sample. The oligonucleotides were then ranked from 1 to 256 based on their r% score. Further calculations were based on the rank of each oligonucleotide with respect to all other oligonucleotides.

The rank of each oligonucleotide was averaged over several experiments (where one experiment is equivalent to testing all 256 test oligonucleotides by the assay of the present invention) in view of the variability in rank between any two experiments. The confidence level for the ranking of the oligonucleotides increased with repetition of the experiment.

Figure 15 shows the results of 4 separate experiments with distamycin. The test samples were treated with 10 μM distamycin for 30 minutes. The r% scores are shown for each of the 4 experiments (labeled 918A, 918B, 1022A, and 1022B) and the ranks of each oligonucleotide in each experiment are shown. The test oligonucleotides have been ranked from 1 to 256 based on their average rank. The average rank was the sum of

the ranks in the individual experiments divided by the number of experiments.

Figures 16 and 17 show the results presented in Figure 15 in graphic form. Figure 16 shows the average ranks plotted against the ideal ranks 1 to 256. Figure 17 shows the average r% scores plotted against the rank of 1 to 256. These data demonstrate the reproducible ability of the assay to detect differential binding and effects of distamycin on different 4 bp sequences.

Example 11

Determining a Consensus Binding Site for Distamycin

One method used to determine the sequence preferences for distamycin was to examine the sequences that rank highest in the assay for sequence similarities. This process may be accomplished visually or by designing computer programs to inspect the data.

Using the data shown in Figure 15, consensus sequences can be constructed for distamycin in the following manner. Sequences with rankings less than 50 (indicating a strong effect of distamycin on the test sequence) in all four experiments were:

TABLE VI

Sequence	Rank
TTCC	1
TTAC	2
TACC	3
TATC	4
TTCG	6
ACGG	8

Sequences with rankings less than 50 (indicating a strong effect of distamycin on the test sequence) in three of the four experiments were:

TABLE VII

Sequence	Rank
AACG	5
TTTC	7
TTAG	10
TAAC	12
TACG	15
AGAC	17
AAAC	18
AGCG	21
AGCC	22
TTCT	24
ACGC	25
AGGG	28
AGGC	30
TTGC	37
ATCG	39
TTTG	43

Sequences with rankings less than 50 (indicating a strong effect of distamycin on the test sequence) in two of the four experiments were:

TABLE VIII

Sequence	Rank
TAGC	9
TTGG	11

Sequence	Rank
AAAG	13
AACC	14
CAAC	16
ATCC	19
AAGG	20
TAAG	23
ACCC	26
TCCC	29
TATG	31
ACCG	32
TCGG	34
AGTC	35
CTCG	38
AATC	44
AGAG	46
TTAA	47
ACAC	48
AGTG	49
TCAC	52

The following assumptions allow prediction of a consensus sequence for a distamycin recognition sequence: (i) the most favored sequences are the test sequences that rank in the top 50 in all four experiments; (ii) the next favored sequences will be the test sequences that rank in the top 50 in 3 of 4 experiments; and (iii) the next favored sequences will be the test sequences that rank in the top 50 in 2 of 4 experiments.

The positions in the test sequence are represented by the numerals 1, 2, 3 and 4. One consensus sequence that predicted from the above binding data is:

1	2	3	4
T	T/A	N	C/G

The nucleotides at each position can also be ranked:

1	2	3	4
T	T>A	C>A>T>G	C>G

Furthermore, the importance of the position of the nucleotide can be ranked. Examination of this data would indicate that the importance of the positions is 1 > 4 > 2 > 3.

These data can be tested for validity by deriving all possible consensus sequences and examining their scores in the assay. The consensus sequences derived from the above information, in order of rank as predicted by the consensus sequence, are:

TABLE IX

Sequence	Predicted Rank	Actual Rank
TTCC	1	1
TACC	2	3
TTCG	3	6
TACG	4	15
TTAC	5	2
TAAC	6	12
TTAG	7	10
TAAG	8	23
TTTC	9	7
TATC	10	4
TTTG	11	43
TATG	12	31

Sequence	Predicted Rank	Actual Rank
TTGC	13	37
TAGC	14	9
TTGG	15	11
TAGG	16	58
	Average rank:	17

Note that the actual rank numbers are out of a possible 256 and that only one number is greater than 50. The average rank of these 16 oligos is only 17. These data indicate that the consensus sequence has predictive value.

Using the same data, a second consensus sequence can be derived that has slightly worse average rank with respect to the relative effect of distamycin in the assay.

TABLE X

1	2	3	4
A	A/G/C	G/C/A	G/C
	A>G=C	C>A=G	G=C

The test sequences predicted by this consensus sequence are as follows:

TABLE XI

Sequence	Actual rank
AACG	5
AACC	14
AAAG	13
AAAC	18
AAGG	20

Sequence	Actual rank
AAGC	74
AGCG	21
AGCC	22
AGAG	46
AGAC	17
AGGG	28
AGGC	30
ACCG	32
ACCC	26
ACAG	73
ACAC	48
ACGG	8
ACGC	25
Ave. rank:	29

This consensus sequence also appears to be predictive of favored distamycin binding sites since the average rank of test oligonucleotides predicted by this sequence is 29, substantially below the median rank of 128. However, the sequences predicted by this consensus sequence do not appear to be affected as strongly by distamycin as the sequences in the first consensus sequence, described above.

Example 12

Testing Actinomycin D to Determine Sequence Specificity and Relative Binding Affinity

A. Ranking of Actinomycin D Sequence Binding Affinities.

Actinomycin D has been tested for sequence selectivity and relative binding affinity to the 256 different 4 bp sequences. The assay was performed essentially as described in Example 10. One assay mixture useful for the testing of actinomycin D contained 1.5 nM radiolabeled DNA and 12.8 nM UL9-COOH protein prepared as described above in the UL9 binding buffer (20 mM Hepes, pH 7.2, 50 mM KCl, and 1 mM dithiothreitol). The concentration of the components can be varied as described in the Detailed Description.

The assay mixtures containing both UL9 and DNA were incubated at room temperature for at least 10 minutes to allow the DNA:protein complexes to form and for the system to come to equilibrium. At time = 0, the assay was begun by adding water (control samples) or actinomycin D (25 μM, test samples) to the assay mixtures using a 12-channel micropipettor. After incubation with drug for 30 minutes, samples were taken and applied to nitrocellulose filters using a 96-well dot blot apparatus (Schleicher and Schuell) held at 4°C. Figure 18 shows the results of 8 screens of actinomycin D.

The % reduction in DNA:protein complex as a result of the presence of actinomycin D is called "r%"; the lower the r% score, the more effective the test molecule in blocking the DNA:protein interaction. For each screen, the test oligonucleotides have been ranked from 1 to 256, based on the r% score; the rank of 1 denotes the lowest r% score (the test oligonucleotide most effected by the test molecule), the rank of 256 denotes

the highest r% score (the test oligonucleotide least effected by the test molecule). The table also shows the average r% score and average rank of each test oligonucleotide; the averages are calculated from the sum of the individual scores and ranks divided by the number of screens, respectively. The test oligonucleotides are then ranked from 1 to 256 based on the average rank in all screens. The final ranking is shown in the two external columns on the table. Test oligonucleotides ranking less than 50 in any individual screen are shown in highlighted boxes.

Figure 19 shows the final rank of test oligonucleotides screened with actinomycin D plotted against the average r% score for these test oligonucleotides.

Figure 20 shows the final ranking vs. the ranks in each individual experiment, the average rank, and the ideal rank.

B. Analysis of the Data Obtained from Ranking Actinomycin D Sequence Binding Affinities.

Several simple analytical procedures may be applied to the data from the screens.

1. Position Effects.

First, to examine possible preferences of the test molecule for a base at any particular position in the test site, the average r% scores are examined. The average r% scores for each of the 64 possible test oligonucleotides at each position in the test site are averaged. For example, to determine the effect of having an A in the first position of the test site, the "A_1" position, the average r% scores for the 64 test oligonucleotides with A in the first position are averaged. The results of this analysis are shown in Figure 21. The mean score for all oligonucleotides in

these screens was r% value 67; the standard deviation was 11.8.

If the r% score is expressed as variance from the mean, as shown in Figure 21, one observes that none of the scores is markedly deviant from the mean. These results suggest that a single base in any particular position has little impact on the binding of the actinomycin D to the test site.

2. Dinucleotide Analysis.

The results of the actinomycin D screen were examined for the presence of dinucleotide pairs that scored well or poorly in the rankings. High scores indicate a preference for the test sequence. Low scores indicate a repulsion of actinomycin D for the test sequence. A dinucleotide analysis is one of many simple analytical procedures that may be applied to the data to extract meaningful impressions about the nature of the sequences to which the test molecule has high affinity.

The data are examined in a manner similar to that used for the single nucleotide analysis. The 16 possible average r% scores for any particular dinucleotide combination are examined. Specific adjacent dinucleotides (N_1N_2, N_2N_3, N_3N_4) or adjacent dinucleotide pairs at any particular position (N_xN_{x+1} = the average of N_1N_2, N_2N_3, and N_3N_4) may be examined, as well as specific dinucleotide pairs that are not adjacent (N_1N_3, N_2N_3, N_1N_4) and any dinucleotide pair separated by one base (N_xN_{x+2} = the average of N_1N_3 and N_2N_3). The means for each set are determined as well as standard deviations.

The difference from the mean (*i.e.*, the mean score less the average r% score for any particular dinucleotide) reflects the extent of deviation from the norm.

Differences from the mean greater than 2-3 standard deviations from the mean are considered to be significant. The data for the dinucleotide analysis of actinomycin D is shown in Figure 22. The differences from the mean are displayed graphically in Figure 23.

In reference to Figures 22 and 23, the dinucleotide preference of actinomycin D is GC, particularly in the N_1N_2 position, but also at any (N_xN_{x+1}) adjacent dinucleotide sequence in the test site.

If the data are combined in a combined bar chart, shown in Figure 24, where the cumulative results for any dinucleotide pair are tabulated in a single bar, the overall observation can be made that actinomycin D prefers GC-rich sequences over AT-rich sequences, with a particular preference for the dinucleotide pairs involving GC.

Example 13

A Method for Selecting Target Sites for DNA-Binding Molecules that are Dimers or Trimers of Distamycin

Once the relative binding preferences of a distamycin have been determined, sequences are selected for target sites for DNA-binding molecules composed of two distamycin molecules, bis-distamycins, or three distamycin molecules, tris-distamycins.

A. Selecting Sequences for Binding with Highest Affinity to Distamycin Oligomers.

The top binding sites for distamycin, determined as described above, are defined by the consensus sequence, 5'-T:T/A:C/A:C-3': accordingly, the top sequences are TTCC, TTAC, TACC and TAAC. Using this information, 2^4 = 16 possible dimer sequences, *i.e.*, combinations of the four top binding sequences, can be

targeted by a bis-distamycin in which the distamycin molecules are immediately adjacent to one another.

The top strands of the 16 possible duplex DNA target sites for binding bis-distamycins are shown in Figure 25. Similarly, trimers of distamycin, tris-distamycins, could be targeted toward selected 12 bp sequences, comprised of all possible combinations of the four 4 bp sequences. There are $3^4 = 81$ possible highest affinity target trimer sequences. There are several advantages to targeting longer sequences with bis- or tris-distamycin:

B. <u>As the Number of Potential Target Sites Decreases, Specificity Increases</u>.

All 8 bp combinatorial possibilities of the 4 top favored binding sites for distamycin are potential high affinity binding sites for bis-distamycin. The consensus sequence used in this example predicts four favored binding sites for distamycin. This represents $(4/4^4)*100$ = about 1.6% of the possible 4 bp sites in the genome. Since there are 4^8 possible 8 bp sequences, this represents, on average, only $(2^4/4^8)*100$ = about 0.02% of the total genome. There are 4^{12} possible 12 bp sequences, this represents, on average, only $(3^4/4^{12})*100 = 0.00000075\%$ of the genome.

The following discussion provides perspective and illustrates the improvement in the actual number of target sites in the human genome for when using a dimer of distamycin versus a monomer of distamycin. The human genome is about 3×10^9 bp. If the number of favored target sites for distamycin is four, and the number of possible 4 bp sequences is $4^4 = 256$, then the number of favored target sites in the genome is $(4/256)(3 \times 10^9) = 4.7 \times 10^7$, or about 50 million favored target sites.

Given that the number of possible 8 bp sites is 4^8 = 65,536, if all possible combinatorial 8 bp sites derived from the favored 4 bp sites ($2^4 = 16$; Figure 25) are favored, then the number of favored 8 bp target sites is $(16/65,536)(3 \times 10^9) = 7.3 \times 10^5$ or about 700,000 possible sites. This represents a 64-fold reduction in the number of highest affinity target sites between distamycin and bis-distamycin; alternatively, this result can be viewed as a 64-fold increase in specificity.

Likewise, given that the number of possible 12 bp sites is $4^{12} = 1.7 \times 10^7$, if all possible favored 12 bp sites ($3^4 = 81$) are favored, then the number of favored 12 bp target sites is $(81/1.7 \times 10^7)(3 \times 10^9) = 1.4 \times 10^4$: *i.e.,* 14,000 possible highest affinity sites. This represents an approximately 3000-fold decrease in the number of highest affinity target sites between distamycin and tris-distamycin and a 500-fold decrease in the number of highest affinity target sites between bis-distamycin and tris-distamycin.

C. <u>An Exponential Increase in Affinity</u>.

As the target site increases in size, (i) the number of target sites in a defined number of nucleotides decreases, and (ii) the specificity increases. Further, the affinity of binding is typically the product of the binding affinities of component parts (see Section VI.E.1 above). As an example, the published binding constant for distamycin to bulk genomic DNA is about $2 \times 10^5\ M^{-1}$. Dimers of distamycin will have a theoretical binding affinity of the square of the binding constant of distamycin: ($K_{dista.average} = 2 \times 10^5 M^{-1}$; $K_{bis\text{-}dista} = (2 \times 10^5 M^{-1})^2 = 4 \times 10^{10}\ M^{-1}$). Trimers of distamycin will have binding

affinities of the cube of the binding affinity of distamycin:

$$(K_{tris\text{-}dista} = (2 \times 10^5 M^{-1})^3 = 8 \times 10^{15}\ M^{-1}).$$

Thus, if distamycin shows only a 10-fold higher affinity ($2 \times 10^6 M^{-1}$) for the top favored binding sites than the average binding sites in DNA, then the affinity constant for bis-distamycin to an 8 bp site comprised of two favored binding sites is 100-fold higher than for an 8 bp sequence comprised of two average binding sites:

$(K_{bis\text{-}dista,\ favored\ sites}/K_{bis\text{-}dista,average\ sites} = (2 \times 10^6)^2/(2 \times 10^5)^2 = 100)$. While this does not represent absolute sequence specificity in binding, the binding affinity is 100-fold greater for 0.02% (16/65,536) of the total possible 8 bp target sequences.

The use of a trimer targeted sequence will afford an even higher increase in affinity to the most favored binding sites:

$K_{tris\text{-}dista,\ favored\ sites}/K_{tris\text{-}dista,average\ sites} = (2 \times 10^6)^3/(2 \times 10^5)^3 = 1000$. Thus, with only 10-fold differential activity in binding between favored sites and average sites, a 1000-fold difference in affinity can be achieved by designing trimer molecules to specific target sites. When considering the administration of DNA-binding molecules as drugs, a 1000-fold lower dose of tris-distamycin, versus the distamycin monomer, could be administered and an increase in relatively specific binding to selected target sites achieved.

In this example, the differential activity of distamycin is only 10-fold. Clearly, differential activities of larger magnitudes will greatly accentuate the increased affinity effect. For example, a 100-fold

difference in activity of a 4 bp DNA-binding molecule toward high affinity and average affinity sequences would result in (i) a 10,000-fold difference in the binding affinity of a dimer of the molecule targeted to an 8 bp sequence, and (ii) a million-fold increase in the binding affinity of the trimer to a 12 bp sequence.

D. <u>Selecting Target Sequences for Distamycin Oligomers with Flexible and/or Variable-Length Linkers in Between the Distamycin Moieties</u>.

The sequences that can be targeted with bis- or tris-distamycin molecules are not limited to sequences in which the two 4 bp favored binding sites are immediately adjacent to one another. Flexible linkers can be placed between the distamycin moieties and sequences can be targeted that are not immediately adjacent. The target sequences can have distances of 1 to several bases between them: this distance depends on the length of the chemical linker. Examples of bis-distamycin target sequences for bis-distamycins with internal flexible and/or variable length linkers targeted to sites comprised of two TTCC sequences are shown in Figure 26, where N is any base.

For each particular bis-distamycin, the explanations of increased affinity and specificity remain the same as described above with the following exception. For the case in which the linker was sufficiently flexible to span different numbers of bases in between the two distamycin sites, the number of sites targeted with highest affinity would be multiplied by the number of bases spanned.

In respect to the ease of drug design and target selection, there are several advantages to the above described targeting strategies, including the following:

i) Any conformational changes induced by binding at the half-site would be minimized.

ii) The affinity, therefore, would be more likely to be the product of the affinities of the interactions observed for the monomeric sites.

iii) The half-molecule (*e.g*, 1 distamycin unit) would anchor the bis-molecule (*e.g.*, bis-distamycin) thus increasing the localized concentration for the binding of the second half of the bis-molecule.

iv) If a simple linking chain is used, with a variable number of atoms, the number of sites that can be targeted by multimers of the monomer increases. This targeting method can be of value when, for example, there are no medically significant target sites with adjacent favored binding sites for distamycin. Therefore there are no good target sites for bis-distamycin. In this situation, the database can be screened for additional target sequences with $N_{1\ to\ n}$ (where N is any base) between the two target binding sequences. For example, where n=4, the number of sequences to be searched becomes $(4^2)*4 = 64$. The likelihood of finding such a sequence is reasonably high.

E. <u>Selecting a Specific Target Site</u>.

Using the above approach, a sequence was identified from the medically significant target site database that contains SEQ ID NO:619, which is a subset of the group of sequences represented by SEQ ID NO:620. SEQ ID NO:619 occurs overlapping the binding site for a transcription factor, Nuclear Factor of Activated T Cells (NFAT-1), which is a major regulatory factor in the induction of interleukin 2 expression early in the T cell activation response. NFAT-1 is crucial in (i) the T cell response, and (ii) in blocking the expres-

sion of IL-2, which causes immunosuppression. The sequences TTCC and TTTC, the distamycin target binding sequences in SEQ ID NO:619, rank first and seventh in the assay.

Example 14

The Use of the Assay in Competition Studies

The assay of the present invention measures the effect of the binding of a DNA-binding molecule to a test site by the release of a protein from an adjacent screening site. Accordingly, the assay is an indirect assay. Following here is the description of an application of the assay useful to provide confirmatory evidence of the data obtained in the initial screening processes.

The results of the distamycin screening assay described in Example 10 suggested that there were possible false negatives: specifically, test sequences that bind distamycin but fail to show an effect on the binding of the reporter protein. The data suggesting false negatives was as follows. If the assay detected strictly the affinity of binding of distamycin, then the scores of the test sequences complementary to the high-scoring test sequences should always be equally high. However, an examination of the highest ranking test sequences and the complementary test sequences reveals that this is not the case (see Table XII).

TABLE XII

Rank	Test Sequence	Complement	Rank of complement
1	TTCC	GGAA	42
2	TTAC	GTAA	244
3	TACC	GGTA	185

Rank	Test Sequence	Complement	Rank of complement
4	TATC	GATA	213
5	AACG	CGTT	144
6	TTCG	CGAA	216
7	TTTC	GAAA	235

All but one of the complementary sequences rank in the lower half, 4 of them in the lowest 20%, *i.e.*, these was little effect on reporter protein binding in the presence of distamycin when using these sequences as test sequences in the assay.

This observation reflects the usefulness of a confirmatory assay that examines the relative affinity of a particular sequence for binding distamycin. A confirmatory assay may also be useful in revealing additional information about the physical characteristics of drug binding. For example, one can hypothesize that the reason for the apparent inverse relationship between test sequences with high activity in the assay and their complements is that the effect of distamycin is directional and only active at one test site. This hypothesis can be tested using the following competition experiment. Competitor oligonucleotides, containing test sequences of interest, are added to the assay mixture. This allows the determination of which test sequences compete most effectively with the radiolabeled test oligonucleotide for binding distamycin.

Assay mixtures are prepared as described in Example 10, using a high-ranking test oligonucleotide, *e.g.*, TTCC (ranking = #1), as the radiolabelled oligonucleotide in the experiment. The test oligonucleotide TTCC is labelled to high specific activity with γ-^{32}P-ATP as described in Example 8: in this example, the

labeled TTCC oligonucleotide will be referred to as the "high specific activity test oligonucleotide".

The competitor oligonucleotides are labeled as described in Example 8, except that the ATP used for kinasing the primer is 1:200 radiolabeled:nonradiolabeled. In other words, the competitor oligonucleotides are tracer labeled with radioactive phosphorous to a 200-fold lower specific activity than the high specific activity test oligonucleotide. Since all of the competitor oligonucleotides are labeled with the same radiolabeled primer molecule, the relative concentrations of the competitor DNAs can be determined with high accuracy. Further, since the specific activity is the same, the concentrations can be adjusted to be the same. For the purposes of this example, the competitor DNAs are referred to as "low specific activity competitor oligonucleotides."

The use of competitor DNAs for which the concentration is known is important for the competition experiment. The accuracy of the competition assay may be further enhanced by separating any unincorporated radiolabeled primer from the double stranded competitor oligonucleotides. This separation can be achieved using, for example, a 6-20% polyacrylamide gel. The gel is then exposed to x-ray film and the amount of double-stranded oligonucleotide determined by use of a scanning laser densitometer, essentially as described in the Examples above.

The competition assay is performed as described in Example 10, except that competitor DNAs are added in increasing relative concentration to the high specific activity test oligonucleotide. The DNA concentration ([DNA]) is held constant and the UL9 concentration ([UL9]) and distamycin concentration ([distamycin]) are

as described in Example 10. The components in the competition assay samples are as follows.

Controls:

UL9 + TTCC*; UL9 + TTCC* + Competitors; UL9 + TTCC* + distamycin;

Test samples:

UL9 + TTCC* + distamycin + Competitors;

where UL9 is UL9-COOH, TTCC* is the high specific activity test oligonucleotide, and Competitors are the low specific activity competitor oligonucleotides.

TTCC-low (the tracer-labeled low specific activity competitor) competes with TTCC* on an equimolar basis for the binding of both protein and distamycin. A competitor molecule with lower affinity for distamycin than TTCC requires a higher molar ratio to TTCC* to compete for distamycin binding. The competition for protein between all competitors is constant. Only the competition for distamycin varies; the variability is due to the differential affinity of the competitor oligonucleotides for distamycin. The concentration of competitor used in these experiments varies over a range of concentrations and is determined empirically by (a) the test molecule concentration, and (b) the relative affinity of the competitor and the radiolabeled test oligonucleotide. Typically, the competitor DNA consists of only the test sequence, that is, no additional sequences are connected to the test sequence.

The competition assay described here facilitates the determination of actual rank between the test oligonucleotides that are detected as highly effective molecules in the original assay. The competition assay also facilitates the detection of false negatives. As described above, the results of the assay discussed in Example 10 imply "directional" binding of distamycin,

in which the effect of binding is only detected when the molecule is bound in one direction with respect to the UL9 protein. Binding in the opposite direction (i.e., to the complementary test sequence) is not detected with the same activity in the assay.

The purpose of this competition experiment is to use the test oligonucleotides to compete for the binding of distamycin. If the sequences complementary to the "best binders" are false negatives in the assay, they should nonetheless be effective competitors in the competition assay.

Example 15

A Method of Selecting Target Sequences From Database Sequence Information

The binding of a drug or other DNA-binding molecule to the recognition sequence for TFIID, or other selected transcription factors, is expected to alter the transcriptional activity of the associated gene. TATA-boxes, which are the recognition sequences for the transcriptional regulatory factor TFIID, are associated with most eukaryotic promoters and are critical for the expression of most eukaryotic genes. Targeting a DNA-binding drug to TATA boxes in general would be undesirable. However, sequences flanking TATA box sequences are typically unique between genes. By targeting such flanking sequences, perhaps with one base overlapping the TFIID recognition site, each gene can be targeted with specificity using the novel DNA-binding molecules designed from the data generated from the DNA-binding drug assay. One method for determining novel and specific target sequences for novel DNA-binding drugs is described here. The method may be applied to any known binding site for any specific transcription

factor, regardless of whether the identity of the transcription factor itself is known.

TATA-boxes have been determined for a large number of genes. Typically, the TATA-box consensus sequence has been identified by examining the DNA sequence 5' of the RNA start site of a selected gene. However, the most rigorous determinations of TATA boxes have also demonstrated the transcription factor binding site by DNA protection experiments and DNA:protein binding assays (using electrophoretic methods). Many of these sites are annotated in the public databases "EMBL" and "GENBANK", which both contain sequences of nucleic acids sequences. Unfortunately, the flat field listing of these databases do not consistently annotate these sites. It is possible, however, to automatically search a database, using a text parsing language called AWK, to extract most sequence information that relates to annotated promoter sequences.

The following is a description of how selected promoter sites were located in the public database from "EMBL." The flat field annotations from "EMBL" Version 32 as processed by "INTELLIGENTICS" (Mountain View, CA), were obtained with the set of UNIX programs call "IG-SUITE." These programs were executed on a "SUN IPX" workstation. An AWK script was used to parse all the primate annotation files listed in the "EMBL" database. The AWK interpreter is supplied as part of the system software that comes with the "SUN IPX" workstation.

The following is a description of how the AWK parses annotation files looking for and printing information relating to promoters and TATA-boxes. The system is asked to examine the input files for certain key words in the header lines or annotations to the sequence. The AWK interpreter reads input files line by

line and executes functions based on patterns found in each line. In this case, the AWK system read the annotation files of EMBL. The following is a description of how the AWK script can be used to parse out sequences containing TATA-boxes.

The program first examines the files for all header lines containing the word "complete" but not "mRNA" or "pseudogene"; the output is printed. Complete genes sometimes contain the promoter sequences but complete mRNA genes do not contain the promoters. mRNA genes are not of interest for the purpose of detecting promoter elements. Next, the AWK system looks for the word "exon 1" and if it finds it prints the header and "DE" line. Then it looks for "5′" and prints the header line if it does not contain the word "mRNA". Next it looks for the word "transcription" and if it finds it prints the preceding and following line along with description line.

Next, the AWK system examines the files for the word "TATA" in the header lines or references. This results is printed. After this it looks for the word "promoter" and if it finds it prints that line and the line after it which contains the information about the promoter. Then the program looks for "protein_bind" and prints that line along with the next one. The description of "protein_bind" is usually used to mark potential binding sites of transcription factors in the "EMBL" database. AWK then scans for any annotated primary mRNA start sites. The promoter sequence is found in front of the start site. Finally, any exon 1 start sites that are annotated in the feature table are extracted. Exon 1 start sites should also be the primary transcription start site and the TATA boxes usually are found approximately 25-35 base pairs 5′ to the transcriptional start site.

The actual AWK script is included here as an example of how to parse a database to extract promoter sites:

```
BEGIN {print_next_line=0}
{if (print_next_line==1)
      {print $0
       print_next_line=0}
}
{if ($0 ~/^>/)
      { Locus=$0
        l_flag=0 }
}
/^>/ && / [Cc]omplete/ && $0 !~ /mRNA¦mrna/ && $0
!~/pseudogene/{print}
/^>/ && /exon 1[^0-9]/ {print}
/^>/ && /5'/ && $0 !~ /mRNA¦mrna/ {print}
/[Tt]ranscription/ {print Locus "\n" PL "\n"
$0;print_next_line=1}
{if ($0 ~/^FT/ && $0 ~/TATA/ && $0 ~/note/)
      {print Locus "\n" PL"\n"$0}
}
{if ($0 ~/^FT/ && $0 ~/[Tt]ranscription/ && $0 ~/\//)
      {print Locus "\n" PL"\n"$0}
}
{if($2 !~ /note/ && $2 ~ /TATA/) {print Locus "\n" $0}
}
{if ($2 ~/promoter/)
      {print_next_line=1
       if(l_flag==0)
          {print Locus "\n" $0
           l_flag=1}
       else
         print $0
      }
}
```

```
{if ($2 ~/protein_bind/)
        {print Locus "\n" $0
         print_next_line=1}
}
{if ($2 ~/prim_transcript/ && $3 !~/^1..|^<1../)
        {print Locus "\n" $0
         print_next_line=1}
}
{if ($0 ~/^FT/ && $0 ~/number=1[^0-9]/)
        if(PL ~/exon/){print Locus "\n" PL"\n"$0}
}
{PL=$0}
```

After the AWK script is run on the database the output is manually examined. Those sites that are clearly promoter sites are noted and nucleotide coordinates recorded. Other gene sequences are examined using the "FINDSEQ" program of "IG_SUITE" to see if the promoter sites can be determined or if the references in the database describe the promoter sequences. If so, those nucleotide coordinates are noted. At the end of this examination "FINDSEQ" is used to extract any sequences containing promoter sequences by using an indirect file of "LOCUS" names constructed using a text editor.

A parsing program was also written to extract each of the annotated sites from the file that "FINDSEQ" extracted from "EMBL." This program extracts the following information: the promoter site name and four numbers representing the nucleotide coordinates of where the sequence is to start, what the coordinate of the first base of the site is, the coordinate of the last base of the site and the end of the sequence to be extracted. A large batch file was constructed to

automatically extract each of the promoter sites. These sequences formed the basis of Table V.

The Sequence Listing presents a number of sequences that are useful as test sequences in the present invention. SEQ ID NO:1 to SEQ ID NO:481 and SEQ ID NO:600 correspond to promoter targets (typically, TATA box-containing sites) for human genes. SEQ ID NO:482 to SEQ ID NO:599 correspond to promoter targets for viral genes.

Example 16

Using Normalized Values to Determine Sequence Specificity and Relative Binding Affinity

A. The Assay Mixture and Calibrator Samples.

The assay mixture is prepared as described in Example 10. The concentration of the components can be varied as described in the Detailed Description.

The assay mixtures containing both UL9 and DNA are incubated at room temperature for at least 10 minutes to allow the DNA:protein complexes to form and for the system to come to equilibrium. At time = 0, the assay is begun by adding water (control samples) or test molecule (typically at 1-5 μM, test samples) to the assay mixtures using a 12-channel micropipettor. After incubation with drug for 5-120 minutes, samples are taken and applied to nitrocellulose filters using a 96-well dot blot apparatus (Schleicher and Schuell) held at 4°C.

Calibrator samples are used to normalize the results between plates, that is, to take plate-to-plate variability into account. Calibrator samples are prepared using 2-fold serial dilutions of DNA in the assay mixture and incubating duplicate samples in one column of the 96-well assay plate. The highest concentration of DNA used is the same concentration

used in the screening samples. In general, calibrator samples are used in all experiments. However, use of calibrator samples appears to be less important for experiments using blocked plates since the variability between blocked plates is lower than between unblocked plates.

The calibrator samples are used to normalize the values between plates as follows. The volume values (Example 10) for the calibrator samples are obtained from densitometry. Volume values are plotted against DNA concentration. The plots are examined to ensure linearity. The volume values for the points on the calibrator line are then averaged for each plate. A factor, designated the normalization factor, is then determined for each calibrator line. When the normalization factor is multiplied by the average of the points on each calibrator line, the product is the same number for all plates. Usually, the average of the line averages is used for determining the normalization factor, although in theory, any of the line average numbers can be used. The operating assumption in this analysis is that the differences in the calibrator samples reflected the differences in adsorption for each plate. By normalizing to the calibrator samples, these variations are minimized.

Once the normalizing factor is obtained, all of the raw volume values for each of the test assays on the plate is multiplied by the normalizing factor. For example, if the following data were obtained, the process of normalization would be as follows:

TABLE XIII

PLATE NUMBER	DNA CONCENTRATION				
	0.8	0.4	0.2	0.1	Average
Plate I:	4000	2000	1000	500	1875
Plate II:	4200	2100	1050	525	1969
Plate III:	3800	1900	950	475	1781
	Average:			1875	

Plate I has a normalization factor of 1; Plate II has a normalization factor of 1875/1969 = 0.95; Plate III has a normalization factor of 1875/1781 = 1.05. The equation used to establish these numbers is as follows: "Average average"/line average = normalization factor.

If the normalization factors are different, these factors are incorporated into the data analysis. The sample data on each plate is then multiplied by the normalization factor to obtain normalized volume values.

B. The Capture/Detection System.

A 96-well dot blot apparatus is typically used to capture the DNA:protein complexes on a nitrocellulose filter as described in Example 10.

C. Quantitation of Data.

The autoradiographs of the nitrocellulose filters are analyzed as described in Example 10.

D. Analysis of Data.

After densitometry, the data is analyzed using a spreadsheet program, such as "EXCEL." For each plate, the calibrator samples are examined and used to determine the normalization value. Then, for each test

oligonucleotide, at each drug concentration and/or each time point, a normalized % score is calculated. The normalized % score (n%) can be described as follows:

$$n\% = (nT/nC) \times 100,$$

where (i) nT is the densitometry volume of the test sample multiplied by the normalization factor for the plate from which the sample was obtained, and (ii) nC is the densitometry volume of the control sample multiplied by the normalization factor for the plate from which the sample was obtained. The oligonucleotides are then ranked from 1 to 256 based on their n% scores.

While the invention has been described with reference to specific methods and embodiments, it will be appreciated that various modifications and changes may be made without departing from the invention.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:
(A) NAME: Genelabs Technologies, Inc.
(B) STREET: 505 Penobscot Drive
(C) CITY: Redwood City
(D) STATE: CA
(E) COUNTRY: USA
(F) POSTAL CODE: 94063

(ii) TITLE OF INVENTION: Sequence-Directed DNA Binding Molecules, Compositions and Methods

(iii) NUMBER OF SEQUENCES: 641

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Genelabs Technologies, Inc.
(B) STREET: 505 Penobscot Drive
(C) CITY: Redwood City
(D) STATE: CA
(E) COUNTRY: USA
(F) ZIP: 94063

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: US 08/123,936
(B) FILING DATE: 17-SEP-1993

(vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: US 07/996,783
(B) FILING DATE: 23-DEC-1992

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Fabian, Gary R.
(B) REGISTRATION NUMBER: 33,875
(C) REFERENCE/DOCKET NUMBER: 4600-0175.41/G19PCT2

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (415) 324-0880
(B) TELEFAX: (415) 324-0960

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human ferredoxin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GCTCTGCTTG CCAATGTCTT TATAGGTCAC CCGGAAGGCA CG 42

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human macrophage alphal-antitrypsin

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

CCTACTGCCT CCACCCGAAG TCTACTTCCT GGGTGGGCAG GAAC 44

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene B for alpha 1-acid glycoprotein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

AGTGACCGCC CATAGTTTAT TATAAAGGTG ACTGCACCCT GCAGCC 46

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for alpha 1 microtubulin-bikunin

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

ATTGGAGCTG TCCTTGGGGC TGTAATTGGC CCCAGCTGAG CAGGGCA 47

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for alpha-2 macroglobulin

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CTGTTTGCAC ACAGAGCAGC ATAAAGCCCA GTTGCTTTGG GAAGT 45

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human ACAA gene for peroxisomal 3-oxoacyl-CoA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

CTCGGGTTTG GCTACAAAAG GTGGAAAGAC TTCCGGTCTG CATTTCTG 48

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human ACAA gene for peroxisomal 3-oxoacyl-CoA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CAAGGTAGGC GGGGCATTGA GTGGAAAGCT CGGCTGGGCG GTGCCTGT 48

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human choline acetyltransferase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GCAATTGTGA CCCACAGCCT AATAATAACA GTCTTTGCCC TCTTGGCC 48

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human angiotensin I-converting enzyme gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

GGCGGGGGTG TGTCGGGTTT TATAACCCGC AGGGCGGCCG CGGCG 45

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene fragment for the acetylcholine receptor gamma

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

GGGGTGGGAG TGTAGGCTGT TATATGACAC CCAGAGCCCA TCTCT 45

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cytokine (Act-2) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GTCCTAGGCC TCAGAGTCCC TATAAAGAGA GATTCCCAAC TCAGTA 46

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human beta-actin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

GGTGAGTGAG CGGCGCGGGG CCAATCGCGT GCGCCGTTCC GAAAG 45

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human beta-actin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GAGCGGCCGC GGCGGCGCCC TATAAAACCC AGCGGCGCGA CGCGCCA 47

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cardiac actin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

TGCTCCAACT GACCCTGTCC ATCAGCGTTC TATAAAGCGG CCCTCCTGGA 50

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for vascular smooth muscle alpha-actin

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

GAGGAGAGCA GGCCAAGGGC TATATAACCC TTCAGCTTTC AGCTTCC 47

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human enteric smooth muscle gamma-actin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

AAGATCCGCC TCTGGGGTTT TATATTGCTC TGGTATTCAT GCCA 44

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human arachidonate 12-lipoxygenase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

GCGGGGCCGC AGACCGGTCC TTTAAAGGTT GGAAGTGGCC CCGAGG 46

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human alcohal dehydrogenase alpha subunit (ADH1) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

GGTGTTATTC AAGCAAAAAA AATAAATAAA TACCTATGCA ATACACCT 48

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human alcohal dehydrogenase beta subunit gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GATGTTACAC AAGCAAACAA AATAAATATC TGTGCAATAT ATCTGCTT 48

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human alpha-fetoprotein gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

TAACAGGCAT TGCCTGAAAA GAGTATAAAA GAATTTCAGC ATGATTTTCC 50

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cytosolic adenylate kinase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

ATGCCGCGCG CTGACAGCCT TATAAATAGT CGCCTTTGCC GGCCGCC 47

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human alpha-N-acetylgalactosaminidase (AK1) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

CGGACTTATC AGGTTACCGG ATTCGAGTCA GAAGCGGCGG CAGGTCTGAA 50

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human ALAD gene for porphobilinogen synthase

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

ATAAAGACCT TTGATCGGAT CTATCATTGT ACCTATCATA GGTCTG 46

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human ALAD gene for porphobilinogen synthase

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

CCCTACCAAG GAGGAAGACT GGATAAAATG GCCTGAGATG GCTGAA 46

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 58 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human albumin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

GAGAGTGACA AAGGCCTGAA TTTGTCAATT AGTAACAATT GTATTCAACA GTAAGGAT 58

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human aldolase A gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

CTGCTCACCA CACACAAGTG TTATAGGAGG AGTCTGGCCC TTGAG 45

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human aldolase C gene for fructose 1,6-bisphosphate aldolase

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

ACCTGCAATA CCCCCTTACC CCAATACCAA GACCAACTGG CATAG 45

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 70 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human aldolase C gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

GGCATAGAGC CAACTGAGAT AAATGCTATT TAAATAAAGT GTATTTAATG AATTTCTCCA 60

AGCTTACGGA 70

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human aldolase A gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

CCTCCACACG TCAACGATTC TATTTGAAGT TGGGCAGGGG GTGGC 45

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 43 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human aldolase A gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

ATTAGAGAAG ATCGGGGACA CATGTGGGGC TGGGCAGGAG CTG 43

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human aldolase A gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

GGGCTGGGCA GGAGCTGCCT TATAACCACC CGGGAACCCC TAGCT 45

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human aldolase A gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

GCGGAGGGCG GAGTGGTGCC TTTAAAAGGC CGGCGCCGCC TTCCGC 46

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human aldolase A gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

TGCGCCGCCC CTTCCGAGGC TAAATCGCTT CCTCTCGGAA CGCGC 45

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: Human aldolase B gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

AAAAAACATG ATGAGAAGTC TATAAAAATT GTGTGCTACC AAAGA 45

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human leukemia inhibitory factor (LIF) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

CTTACAACAC AGGCTCCAGT ATATAAATCA GGCAAATTCC CCATTTGAGC 50

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO
(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human aminopeptidase N gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GGGGCTCCTC CCCTTTGGGG ATATAAGCCC GGCCTGGGGC TGCTCC 46

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human alpha-amylase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

AAATGTGCTT CTTACAGGAA TATAAATAGT TTCTGGAAAG GACACTG 47

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human amyloid-beta protein gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

GGGAGGCCTG CGGGGTCGGA TGATTCAAGC TCACGGGGAC GAGCAGG 47

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 54 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human amyloid beta protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

CGGGGACGAG CAGGAGCGCT CTCGACTTTT CTAGAGCCTC AGCGTCCTAG GACT 54

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human amyloid-beta protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

GCGGGGTGGG CCGGATCAGC TGACTCGCCT GGCTCTGAGC CCCGCCG 47

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human amyloid-beta protein (APP) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

TCAGCTGACT CGCCTGGCTC TGAGCCCCGC CGCCGCGCTC GGGCTCCGTC 50

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human pronatriodilatin precursor gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

TGCTTGGAGA GCTGGGGGGC TATAAAAAGA GGCGGCACTG GGCAGC 46

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for atrial natriuretic factor

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

TTGAAGTGGG AGCCTCTTGA GTCAAATCAG TAAGAATGCG GCTCTTGCA 49

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for atrial natriuretic factor

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

CTGCGGATGA TAACTTTAAA AGGGCATCTC CTGCTGGCTT CTCACTTGG 49

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for atrial natriuretic factor

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

TGCTTGGAGA GCTGGGGGGC TATAAAAAGA GGCGGCACTG GGCAGC 46

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human atrial natriuretic factor

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

CTTGGAGAGC TGGGGGGCTA TAAAAAGAGG CGGCACTGGG CAGCTGGGAG 50

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human angiotensinogen gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

CTCCATCCCC ACCCCTCAGC TATAAATAGG GCCTCGTGAC CCGGCC 46

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human heart/skeletal muscle ATP/ADP translocator gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

TCGCGAGAGC CCGGCGGGGA TATAAGGGGG AGCTGCGGGC CAGGC 45

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human apolipoprotein CIII gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

TCTGGACACC CTGCCTCAGG CCCTCATCTC CACTGGTCAG CAGGTGACC 49

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human apolipoprotein CIII gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

CTCAGGCCCT CATCTCCACT GGTCAGCAGG TGACCTTTGC CCAGCGCCC 49

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human apolipoprotein CIII gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

TGCCTGCTGC CCTGGAGATG ATATAAAACA GGTCAGAACC CTCCTGCC 48

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human apolipoprotein CIII gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

GACACCCTGC CTCAGGCCCT CATCTCCACT GGTCAGCAGG TGACCTTTGC 50

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human apolipoprotein CIII gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

TGCCTGCTGC CCTGGAGATG ATATAAAACA GGTCAGAACC CTCCTGCC 48

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human apolipoprotein AII gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

ATAATCCCTG CCCCACTGGG CCCATCCATA GTCCCTGTCA CCTGACAGG 49

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human apolipoprotein AII gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

GGGGTGGGTA AACAGACAGG TATATAGCCC CTTCCTCTCC AGCCAG 46

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human fetal gene for apolipoprotein AI precursor

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

CTGCAGACAT AAATAGGCCC TGCAAGAGCT GGC 33

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human apolipoprotein B gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

GCCTGGGCTT CCTATAAATG GGGTGCGGGC GCCGGCCGC 39

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human apoC-II gene for preproapolipoprotein C-II

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

CGGAAGTGGG TCTCAACCAC TATAAATCCT CTCTGTGCCC GTCCGGA 47

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human apolipoprotein C-I (VLDL) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

TGCCCCGCCC CTCCCCAGCC TGATAAAGGT CCTGCGGGCA GGACAGG 47

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human apolipoprotein D gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

ATCAGAGACC TGAAGAAGCT TATAAAATAG CTTGGGAGAG GCCAGTC 47

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human arginase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

GGTTGTTTAT TCAACCCAAG TATAAATGGA AAAAAAAGAT GCGCC 45

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human argininosuccinate synthetase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

CTGCCCCCGG GCCCTGTGCT TATAACCTGG GATGGGCACC CCTGC 45

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human sodium/potassium ATPase alpha 3 subunit (ATP1 A3)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

CCCCTCCCGC GGACGCGGGC ATATGAGGAG GCGGAGGCGG CGGC 44

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human (BSF-2/IL6) gene for B cell stimulatory factor-2

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

ATTAGAGTCT CAACCCCCAA TAAATATAGG ACTGGAGATG TCTGAGGC 48

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human C5 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

TCTGAATTCT TCAAGTTCAG TTTATTTAAA AGGAGACTAT CCTCAAAAGT G 51

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human carbonic anhydrase II gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

CCTCCCCTTG TCGCCTAGGT CCACCCGAGC CCCCTCCCCC GGGCC 45

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human carbonic anhydrase II gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

GCACGAAGTT GGCGGGAGCC TATAAAAGCG GGCCGGCGCG ACCCGC 46

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human calcitonin/alpha-CGRP gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

TTCCCGACCC ACAGCGGCGG GAATAAGAGC AGTCGCTGGC GCTGG 45

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human calretinin gene, exon 1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

CAGGCGCAGG CTCCAGAGCG TATATAAGGG CAGCGTGGCG CACAACC 47

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cathepsin G gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

TTCCTTCCTC TCTCAGGGCC TTAAAGTCTA GGAGGAGGAA GCACA 45

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human carbonic anhydrase VII (CA VII) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

CTCCTCCCGC CAGCCGCTGC TTTAAGAGGC TGCTCCGCGG TAGCG 45

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cardiac beta myosin heavy chain gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

TCTAGTGACA ACAGCCCTTT CTAAATCCGG CTAGGGACTG GGTGCC 46

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cardiac beta myosin heavy chain gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

TGGGGGTGCC TGCTGCCCCA TATATACAGC CCCTGAGACC AGGTC 45

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human complement C3 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

TGGGGGAAAG CAGGAGCCAG ATAAAAAGCC AGCTCCAGCA GGCGCTG 47

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human recognition/surface antigen (CD4) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

CAAGTCCTCA CACAGATACG CCTGTTTGAG AAGCAGCGGG CAAGAAAGAC 50

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human hyaluronate receptor gene (CD44)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

TAGGTCACTG TTTTCAACCT CGAATAAAAA CTGCAGCCAA CTTCCGAGGC 50

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cystic fibrosis transmembrane conductance reg. gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

AATGACATCA CAGCAGGTCA GAGAAAAAGG GTTGAGCGGC AGGCACCCAG 50

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cholesterol 7-alpha-hydroxylase (CYP7) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

ATGGATCTGG ATACTATGTA TATAAAAAGC CTAGCTTGAG TCTCTT 46

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human choline acetyltransferase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

AGCAATTGTG ACCCACAGCC TAATAATAAC AGTCTTTGCC CTCTTGGCC 49

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human mast cell chymase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

CTCTCTTGCC TTCTAGGAGT TATAAAACCC AAGACTGGAA AGGAAA 46

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human heart chymase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

CCTCTCTTGC CTTCTGGGAG TTATAAAACC CAAGACTGGA AGGAAAA 47

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human creatine kinase B gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

GGCCAATGGA ATGAATGGGC TATAAATAGC CGCCAATGGG CGGCCCGC 48

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human C-type natriuretic peptide gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

ACATCAGCGG CAGGTTGGAT TATAAAGGCG CGAGCAGAGT CACGGG 46

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human transmembrane protein (CD59) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

GCTCCGCGCG GGGGTGGAGG GAGAGGAGGA GGTTCCTGCC GAGGT 45

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human transmembrane protein (CD59) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

GAGGGCAAGG GCATCCTGAG GGGCGGGGCC GGGGGCGGAG CCTTGC 46

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human transmembrane protein (CD59) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

ATCCTGAGGG GCGGGGCCGG GGGCGGAGCC TTGCGGGCTG GAGCCGA 46

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human transmembrane protein (CD59) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

TGAGGGGCGG GGCCGGGGGC GGAGCCTTGC GGGCTGGAGC GAAAGAATGC 50

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human myeloid specific CD11b gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

GCCCTCTTCC TTTGAATCTC TGATAGACTT CTGCCTCCTA CTTCTC 46

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cholesteryl ester transferase protein (CETP) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

GTGGGGGCTG GGCGGACATA CATATACGGG CTCCAGGCTG AACGGC 46

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cystic fibrosis transmembrane conductance regulator

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

TGGGTGGGGG GAATTGGAAG CAAATGACAT CACAGCAGGT CAGAG 45

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cystic fibrosis transmembrane conductance regulator

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

GTGGGGGGAA TTGGAAGCAA ATGACATCAC AGCAGGTCAG AGAAAAA 47

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human coseg gene for vasopressin-neurophysin precursor

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

CACGGGAACA CCTGCGGACA TAAATAGGCA GCCAGCAGAG GCAGCA 46

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human creatine kinase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

TTCAGAGAAA GGGCAGGTGC TATAAAGGGC CCAGCGCCAC GGGCCT 46

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human alpha-B-crystallin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

AGAAGCTTCA CAAGACTGCA TATATAAGGG GCTGGCTGTA GCTGCAG 47

(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human C3 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

AGTGGGGGAA AGCAGAGCCA GATAAAAAGC CAGCTCCAGC AGGCGCTGCT 50

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human colony stimulating factor CSF-1 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

GCCTGGCCAG GGTGATTTCC CATAAACCAC ATGCCCCCCA GTCCTC 46

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cytotoxic serine proteinase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

GTTACTCAGC AGCAGGGGTG TAAATGTGAC AGTGCCATGT CAAC 44

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human CST3 gene for cystatin C

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

GGCGGCGAAG GCCGGAAGGG ATAAAACCGC AGTCGCCGGC CTCGCG 46

(2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human CST4 gene for Cystatin D

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

TTGGGGGACA CCCAAGTAGG ATAAATGCAC AGCTAGCTTC TGGCC 45

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human CYP2C8 gene for cytochrome P-450

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

ACTAAATTAG CAGGGAGTGT TATAAAAACT TTGGAGTGCA AGCTC 45

(2) INFORMATION FOR SEQ ID NO:101:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cholesterol desmolase cytochrome gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

AGCAGGAGGA AGGACGTGAA CATTTTATCA GCTTCTGGTA TGGCC 45

(2) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cholesterol desmolase cytochrome P-450 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

TATGGCCTTG AGCTGGTAGT TATAATCTTG GCCCTGGTGG CCCAGG 46

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human steriod 11-beta-hydroxylase (CYP11B1) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

GAAGGCAAGG CACCAGGCAA GATAAAAGGA TTGCAGCTGA ACAGGGT 47

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human CYPXI gene for steroid 18-hydroxylase (P-450 C18)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

CAGAGCAGGT TCCTGGGTGA GATAAAAGGA TTTGGGCTGA ACAGGGT 47

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human CYPXIX aromatase P-450 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

TGGACAATAA ATGAAATCTC CATAAAAGGC CCAAAGGACA GGGTTC 46

(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human decay-accelerating factor (DAF) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

AGCCCAGACC CCGCCCAAAG CACTCATTTA ACTGGTATTG CGGAGC 46

(2) INFORMATION FOR SEQ ID NO:107:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human dopamine beta-hydroxylase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

ACGTCCATGT GTCATTAGTG CCAATTAGAG GAGGGCAGCA GGCTG 45

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human dopamine beta-hydroxylase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

ACCCCATTCA GGACCAGGGC ATAAATGGCC AGGTGGGACC AGAGAG 46

(2) INFORMATION FOR SEQ ID NO:109:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human desmin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

GGGGCTGATG TCAGGAGGGA TACAAATAGT GCCGACGGCT GGGGGC 46

(2) INFORMATION FOR SEQ ID NO:110:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cytokeratin 8 (CK8) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

CCCGGGGCTG GGATCTCTTT TATAAAAGGC CATTCCTGAG AGCTC 45

(2) INFORMATION FOR SEQ ID NO:111:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human DNA polymerase alpha gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

GCCTCCCGAG CCGCTGATTG GCTTTCAGGC TGGCGCCTGT CTCGGCCCCC 50

(2) INFORMATION FOR SEQ ID NO:112:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human dopamine D1A receptor gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:

GCTGTGCCCC CCGGGAACCC CGCCGGCCTG TGCGCTTGCT GGTGCCAGCT 50

(2) INFORMATION FOR SEQ ID NO:113:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human eosinophil cationic protein (ECP) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

AGACCCACCA AGGGAAGCTT TATTTAAACA GTTCCAAGTA GGGGAGA 47

(2) INFORMATION FOR SEQ ID NO:114:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human HER2 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:

GAGGAGGAGG GCTGCTTGAG GAAGTATAAG AATGAAGTTG TGAAGCTGAG 50

(2) INFORMATION FOR SEQ ID NO:115:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human elastin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:

GTGTCTCGCT GTGATAGATC AATAAATATT TTATTTTTTG TCCTGG 46

(2) INFORMATION FOR SEQ ID NO:116:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human endothelial leukocyte adhesion molecule I (ELAM-1)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:

ATTCACAGGA AGCAATCCCT CCTATAAAAG GCCCTCAGCC GAAGTAGTG 49

(2) INFORMATION FOR SEQ ID NO:117:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human eosinophil major basic protein gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:

GGAAGTTCCT CCAAGGCCTC TATATAAGAA GTCTTTGTGA GAGGAAG 47

(2) INFORMATION FOR SEQ ID NO:118:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human preproenkephalin B gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

CTCTAGGAAA GTTTCTCAGC TCTCAAACCT CTGTTTTCTC ATCTGCAAG 49

(2) INFORMATION FOR SEQ ID NO:119:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human preproenkephalin B gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

TTCTCATCTG CAAGATGGGG ATAATATTAA CCAACTGGCT AGGTCATGAG 50

(2) INFORMATION FOR SEQ ID NO:120:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human ENO3 gene for muscle-specific enolase

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:

GGGGACCGAG TGGCTCAGGG ATAAATGCGC ACCTGAGAGG GGGTGA 46

(2) INFORMATION FOR SEQ ID NO:121:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human eosinophil derived neurotoxin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

CAACCCACCA AGGGATGCTT TATTTAAACA GTTCCAAGTA GGGGAGA 47

(2) INFORMATION FOR SEQ ID NO:122:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human erythropoietin receptor

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:

TACCCAGGCT GAGTGCTGGC CCCGCCCCCT CGGGGATCTG CCACTT 46

(2) INFORMATION FOR SEQ ID NO:123:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human c-erb B2/neu protein gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

AGGAGGGCTG CTTGAGGAAG TATAAGAATG AAGTTGTGAA GCTGA 45

(2) INFORMATION FOR SEQ ID NO:124:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human ERCC2 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

CCGATTGGCT CTGCCCTAGC GGATTGACGG GCAGGTTAGC CAATGGTCT 49

(2) INFORMATION FOR SEQ ID NO:125:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human ERCC2 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

CAGGTTAGCC AATGGTCTCG TAATATAGGT GGAGCGAGCC CTCGAGG 47

(2) INFORMATION FOR SEQ ID NO:126:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human erythropoietin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

GGTCACCCGG CGCGCCCCAG GTCGCTGAGG GACCCCGGCC AGGCGCGGAG 50

(2) INFORMATION FOR SEQ ID NO:127:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human oestrogen receptor

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

ATATGAGCTC GGGAGACCAG TACTTAAAGT TGGAGGCCCG GGAGCCCA 48

(2) INFORMATION FOR SEQ ID NO:128:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human elastase I gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:128:

AGCTTTGCTG CTAAGAGGAG TATAAAGAGG GCTTGGTCCA AGCAAG 46

(2) INFORMATION FOR SEQ ID NO:129:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human fibrinogen gamma chain gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:129:

GGCCCCGTGA TCAGCTCCAG CCATTTGCAG TCCTGGCTAT CCCA 44

(2) INFORMATION FOR SEQ ID NO:130:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human fibrinogen gamma chain gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:130:

TGGCTATCCC AGGAGCTTAC ATAAAGGGAC AATTGGAGCC TGAGA 45

(2) INFORMATION FOR SEQ ID NO:131:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human lymphocyte IgE receptor gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:

TTAACATCTC TAGTTCTCAC CCAATTCTCT TACCTGAGAA ATGGA 45

(2) INFORMATION FOR SEQ ID NO:132:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human lymphocyte IgE receptor gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:132:

GTTATCCGGG TGGCAAGCCC ATATTTAGGT CTATGAAAAT AGAAGCT 47

(2) INFORMATION FOR SEQ ID NO:133:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human lymphocyte IgE receptor gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:133:

AGCCCATATT TAGGTCTATG AAAATAGAAG CTGTCAGTGG CTCTAC 46

(2) INFORMATION FOR SEQ ID NO:134:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human apoferritin H gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:134:

GGGCCTGACG CCGACGCGGC TATAAGAGAC CACAAGCGAC CCGCA 45

(2) INFORMATION FOR SEQ ID NO:135:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human fibrinogen beta gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

TATTAACTAA GGAAAGGTAA CCATTTCTGA AGTCATTCCT AGCAGA 46

(2) INFORMATION FOR SEQ ID NO:136:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human fibrinogen beta gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:136:

ATTCCTAGCA GAGGACTCAG ATATATATAG GATTGAAGAT CTCTCAGTT 49

(2) INFORMATION FOR SEQ ID NO:137:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human factor IX gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:

CCAGAAGTAA ATACAGCTCA GCTTGTACTT TGGTACAACT AATCGACCTT 50

(2) INFORMATION FOR SEQ ID NO:138:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human FK506 binding proteins 12A, 12B, and 12C (FKBP12)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:138:

GAGCCGTGGA ACCGCCGCCA GGTCGCTGTT GGTCCACGCC GCCCGTCGCG 50

(2) INFORMATION FOR SEQ ID NO:139:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human 5-lipoxygenase activating protein (FLAP) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:139:

TTGTGCCGGG GATCTTCAGA AATTGTAATG ATGAAAGAGT GCAAGCTCTC 50

(2) INFORMATION FOR SEQ ID NO:140:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human fos proto-oncogene (c-fos)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:140:

ATTCATAAAA CGCTTGTTAT AAAAGCAGTG GCTGCGGCGC CTCGTACTCC 50

(2) INFORMATION FOR SEQ ID NO:141:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human GOS2 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:141:

GGCGTGTCTC AGAGAAAAGA TATAAGCGGC CCCCGGACGC TAAAG 45

(2) INFORMATION FOR SEQ ID NO:142:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human granulocyte colony-stimulating factor gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:142:

CAGGCCTCCA TGGGGTTATG TATAAAGGGC CCCCTAGAGC TGGGCC

(2) INFORMATION FOR SEQ ID NO:143:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human EGR2 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:143:

CGGGTATTGA AGACCTGCCC ATAAATACTT AGAGCAACAC TTTCCGTC 48

(2) INFORMATION FOR SEQ ID NO:144:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human growth hormone (hGH) gene

RIPTION: SEQ ID NO:144:

TATAAAAAGG GCCCACAAGA GACCAG 46

SEQ ID NO:145:

ARACTERISTICS:
: 50 base pairs
(B) nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gastric inhibitory polypeptide (GIP) mRNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:145:

TAATCAGCAG GTCTATGCCT AATATAAAGG AGCTGGGGCA TGATTTCTTC 50

(2) INFORMATION FOR SEQ ID NO:146:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human GLA gene for alpha-D-galactosidase A

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:146:

GAAACAATAA CGTCATTATT TAATAAGTCA TCGGTGATTG GTCCGC 46

(2) INFORMATION FOR SEQ ID NO:147:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human glucagon gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:147:

TTTACAGATG AGAAATTTAT ATTGTCAGCG TAATATCTGT GAGG 44

(2) INFORMATION FOR SEQ ID NO:148:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human glucagon gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:148:

GGCTAAACAG AGCTGGAGAG TATATAAAAG CAGTGCGCCT TGGTGCA 47

(2) INFORMATION FOR SEQ ID NO:149:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human granulocyte-macrophage colony stimulating factor gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:149:

CATTAATCAT TTCCTCTGTG TATTTAAGAG CTCTTTTGCC AGTGAGC 47

(2) INFORMATION FOR SEQ ID NO:150:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human glucocorticoid receptor gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:150:

TGGGCAATGG GAGACTTTCT TAAATAGGGC TCTCCCCCCA CCCATG 46

(2) INFORMATION FOR SEQ ID NO:151:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human growth hormone releasing factor (GRF) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:151:

AACGCTTAGG AAAATGAAGA GATAAATGAT GGGAACGCCA GGCGGCTGCC 50

(2) INFORMATION FOR SEQ ID NO:152:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human GST pi gene for glutathione S-transferase pi

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:152:

GAGCGGGGCG GGACCACCCT TATAAGGCTC GGAGGCCGCG AGGC 44

(2) INFORMATION FOR SEQ ID NO:153:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: human glycophorin C (GPC) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:153:

CAGAAGTGGG CGGGTGTGTG TTTAAAAAAA AAAAAAGGGG TGGAAAC 47

(2) INFORMATION FOR SEQ ID NO:154:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human histone (H10) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:154:

CGCGGTCCGC CCGCCGCCGC TAAATACCCG GATGCGCCGC CCAAGC 46

(2) INFORMATION FOR SEQ ID NO:155:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for H1 RNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:155:

GTCTTTGGAT TTGGGAATCT TATAAGTTCT GTATGAGACC ACTC 44

(2) INFORMATION FOR SEQ ID NO:156:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human H1 histone gene FNC16

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:156:

GGCGGTGGAT TGGACGCTCC ACCAATCACA GGGCAGCGCC GGCTTA 46

(2) INFORMATION FOR SEQ ID NO:157:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 54 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human histone gene FNC16

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:157:

ACCAATCACA GGGCAGCGCC GGCTTATATA AGCCCGGGCC CGAGCATAGC AGCA 54

(2) INFORMATION FOR SEQ ID NO:158:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human H2B.2 and H2A.1 genes for Histone H2A and H2B

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:158:

TTTTCGCGCC CAGCAGCTGC TATAAAATGC GCGTCCCTGT AGGTTCC 47

(2) INFORMATION FOR SEQ ID NO:159:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human H4/a gene for H4 histone

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:159:

GGGGGCAGGG GTAACGTAGA TATATAAAGA TCGGTTTCCT ATTCTCTC 48

(2) INFORMATION FOR SEQ ID NO:160:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 56 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human H4/b gene for H4 histone

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:160:

CTGCAAGTAT AGTGTGTGTG TATATATATA TATATACCTA GCAGTATTTA TTAAAT 56

(2) INFORMATION FOR SEQ ID NO:161:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human androgen receptor gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:161:

GGTGGGGGCG GGACCCGACT CGCAAACTGT TGCATTTGCT CTCCACCTCC 50

(2) INFORMATION FOR SEQ ID NO:162:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human chorionic gonadotropin (hCG) beta subunit

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:162:

GCCCTCTCTC ATTGGGCAGA AGCTAAGTCC GAAGCCGCGC CCCTCCTGG 49

(2) INFORMATION FOR SEQ ID NO:163:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human islet amyloid polypeptide (hIAPP) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:163:

GCTGAGAAAG GTGTGAGGGG TATATAAGAG CTGGATTACT AGTTAGCAAA 50

(2) INFORMATION FOR SEQ ID NO:164:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 52 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human H4 histone gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:164:

CTTCCCGCCG GCGCGCTTTC GGTTTTCAAT CTGGTCCGAT ATCTCTGTAT AT 52

(2) INFORMATION FOR SEQ ID NO:165:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human H4 histone gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:165:

AATCTGGTCC GATATCTCTG TATATTACGG GGAAGACGGT GACGCTC 47

(2) INFORMATION FOR SEQ ID NO:166:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human histone H2a gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:166:

TCCTCTTTTC TTGGCGAACT CAACTGGTAT GAATTCCTCA 40

(2) INFORMATION FOR SEQ ID NO:167:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human histone H2a gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:167:

CACAGCCTAC CTCCAGTCAG TATAAATACT TCTCTGCCTT GCGTTC 46

(2) INFORMATION FOR SEQ ID NO:168:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human histone H2b gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:168:

TATTTGCATA AGCGATTCTA TATAAAAGCG CCTTGTCATA CCCTGCT 47

(2) INFORMATION FOR SEQ ID NO:169:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human histone H3 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:169:

ATTTTTGAAT TTTCTTGGGT CCAATAGTTG GTGGTCTGAC TCTAT 45

(2) INFORMATION FOR SEQ ID NO:170:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human histone H3 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:170:

CAATAGTTGG TGGTCTGACT CTATAAAAGA AGAGTAGCTC TTTCCTT 47

(2) INFORMATION FOR SEQ ID NO:171:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human HLA-A1 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:171:

AGTGTCGTCG CGGTCGCTGT TCTAAAGTCC GCACGCACCC ACCGG 45

(2) INFORMATION FOR SEQ ID NO:172:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human HLA-B27 antigen gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:172:

AGTGTCGCCG GGGTCCCAGT TCTAAAGTCC CCACGCACCC ACCCGG 46

(2) INFORMATION FOR SEQ ID NO:173:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human HLA-Bw57 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:173:

AGCGTCGCCG CGGTCCCAGT TCTAAAGTCC CCACGCACCC ACCCG 45

(2) INFORMATION FOR SEQ ID NO:174:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human HLA-F gene for human leukocyte antigen F

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:174:

TGTCGCCGCA GTTCCCAGGT TCTAAAGTCC CACGCACCCC GCGGGA 46

(2) INFORMATION FOR SEQ ID NO:175:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for histocompatibility antigen HLA-A3

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:175:

AGTGTCGTCG CGGTCGCTGT TCTAAAGCCC GCACGCACCC ACCGGG 46

(2) INFORMATION FOR SEQ ID NO:176:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for class I histocompatibility antigen HLA-CW3

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:176:

CATTGGGTGT CGGACCTCTA GAAGGCCGGT CAGCGTCTCC GC 42

(2) INFORMATION FOR SEQ ID NO:177:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human HMG-17 gene for non-histone chromosomal protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:177:

CGGTCCGGGG CTCCCAGCGC TATAAAAACT TTATAAACCC CCCGGA 46

(2) INFORMATION FOR SEQ ID NO:178:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human HOX3D gene for homeoprotein HOX3D

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:178:

AAGAAAGAGA TATCTCCACC TATAAATTGT CCACTTTGGA GAACAA 46

(2) INFORMATION FOR SEQ ID NO:179:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human 71Kd heat shock cognate protein (hsc70)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:179:

TGGAAGGTTC TAAGATAGGG TATAAGAGGC AGGGTGGCGG GCGGA 45

(2) INFORMATION FOR SEQ ID NO:180:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human heat shock protein (hsp 70) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:180:

AAGGCGGGTC TCCGTGACGA CTTATAAAAG CCCAGGGGCA AGCGGTCCGG 50

(2) INFORMATION FOR SEQ ID NO:181:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human hsp70B gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:181:

CTTCGGTCTC ACGGACCGAT CCGCCCGAAC CTTCTCCCGG GGTCAG 46

(2) INFORMATION FOR SEQ ID NO:182:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human hsp70B gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:182:

CCGCCCGGCT GACTCAGCCC GGGCGGGCGG GCGGGAGGCT CTCGAC 46

(2) INFORMATION FOR SEQ ID NO:183:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: YES

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human hsp70B gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:183:

CCGGCTGACT CAGCCCGGGC GGGCGGGCGG GAGGCTCTCG ACTGGG 46

(2) INFORMATION FOR SEQ ID NO:184:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human hsp70B gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:184:

CTGACTCAGC CCGGGCGGGC GGGCGGGAGG CTCTCGACTG GGCGGG 46

(2) INFORMATION FOR SEQ ID NO:185:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human hsp70B gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:185:

GGGCGGGCGG GAGGCTCTCG ACTGGGCGGG AAGGTGCGGG AAGGT 45

(2) INFORMATION FOR SEQ ID NO:186:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 53 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human hsp70B gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:186:

CGGCGGGGTC GGGGAGGTGC AAAAGGATGA AAAGCCCGTG GACGGAGCTG AGC 53

(2) INFORMATION FOR SEQ ID NO:187:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human IAPP gene for islet amyloid polypeptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:187:

GCTGAGAAAG GTGTGAGGGG TATATAAGAG CTGGATTACT AGTTAGC 47

(2) INFORMATION FOR SEQ ID NO:188:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human intercellular adhesion molecule 1 (ICAM-1) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:188:

AGGTTTCCGG GAAAGCAGCA CCGCCCCTTG GCCCCCAGGT GGCTAG 46

(2) INFORMATION FOR SEQ ID NO:189:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human intercellular adhesion molecule 1 (ICAM-1) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:189:

GGCCCCCAGG TGGCTAGCGC TATAAAGGAT CACGCGCCCC AGTCGA 46

(2) INFORMATION FOR SEQ ID NO:190:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human interferon-inducible gene IFI-54K

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:190:

AAAGGAACCA GAGGCCACTG TATATATAGG TCTCTTCAGC ATTTATTG 48

(2) INFORMATION FOR SEQ ID NO:191:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human interferon alpha gene IFN-alpha 14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:191:

ATGGAAGCTA GTATGTTCCT TATTTAAGAC CTATGCACAG AGCAAGGT 48

(2) INFORMATION FOR SEQ ID NO:192:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human interferon alpha gene IFN-alpha 16

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:192:

GAAATTAGTA TGTTCACTAT TTAAGAACTA TGCACAGAGC AAAGT 45

(2) INFORMATION FOR SEQ ID NO:193:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human interferon alpha gene IFN-alpha 5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:193:

ATGGAAACTC GTATGTGACC TTTTTAAGAT CTGTGCACAA AACAAGGT 48

(2) INFORMATION FOR SEQ ID NO:194:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human interferon alpha gene IFN-alpha 6

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:194:

ATGGAAACTA GTATGTTCCC TATTTAAGAC CTACACATAA AGCAAGGT 48

(2) INFORMATION FOR SEQ ID NO:195:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human interferon alpha gene IFN-alpha 7

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:195:

ATGGAAATTA GTATGTTCAC TATTTAAGAC CTATGCACAG AGCAAAGT 48

(2) INFORMATION FOR SEQ ID NO:196:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human immune interferon (INF-gamma) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:196:

TCCTCAGGAG ACTTCAATTA GGTATAAATA CCAGCAGCCA GAGGAGGTGC 50

(2) INFORMATION FOR SEQ ID NO:197:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human alpha/beta-interferon (IFN)-inducible 6-16 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:197:

GGGAGGATCC ACAAGTGATG ATAAAAAGCC AGCCTTCAGC CGGAG 45

(2) INFORMATION FOR SEQ ID NO:198:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human insulin like growth factor II (IGF-2)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:198:

CTGGGAGGAG TCGGCTCACA CATAAAAGCT GAGGCACTGA CCAGCCT 47

(2) INFORMATION FOR SEQ ID NO:199:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human insulin-like growth factor binding protein gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:199:

GTGGCGCGGC CTGTGCCCTT TATAAGGTGC GCGCTGTGTC CAGCG 45

(2) INFORMATION FOR SEQ ID NO:200:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human germline leader peptide and variable region of 1154

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:200:

CAACCTCCTG CACTGAAGCC TTATTAATAG GCTGGCCACA CTTCATGC 48

(2) INFORMATION FOR SEQ ID NO:201:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human germline for leader peptide & variable region of 2908

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:201:

CAACCTCCTG CCCTGAAGAC TTATTAATAG GCTGGACACA CTTCATGC 48

(2) INFORMATION FOR SEQ ID NO:202:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human rearranged kappa immunoglobulin subgroup V

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:202:

CCACGACCAG GTGTTTGGAT TTTATAAACG GGCCGTTTGC ATTGTGAA 48

(2) INFORMATION FOR SEQ ID NO:203:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human rearranged kappa immunoglobulin gene subgroup V

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:203:

CGCCCTGCAG TCCAGAGCCC ATATCAATGC CTGGGTCAGA GCTCTGGA 48

(2) INFORMATION FOR SEQ ID NO:204:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human germline fragment for immunoglobulin kappa light chain

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:204:

TGCCCTACCT TCCAGAGCCC ATATCAATGC CTGTGTCAGA GCCCTGGG 48

(2) INFORMATION FOR SEQ ID NO:205:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human germline immunoglobulin kappa light chain V-segment

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:205:

ACTTCCCTTG TGGGTCTGAG ATAAAAGCTC AGCTCTAACC CTTACC 46

(2) INFORMATION FOR SEQ ID NO:206:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human interleukin-2 (IL-2) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:206:

TATTTTTCCA GAATTAACAG TATAAATTGC ATCTCTTGTT CAAGAG 46

(2) INFORMATION FOR SEQ ID NO:207:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for interleukin 1 alpha (IL-1 alpha)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:207:

CCACGCCTAC TTAAGACAAT TACAAAAGGC GAAGAAGACT GACTCAG 47

(2) INFORMATION FOR SEQ ID NO:208:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for prointerleukin 1 beta

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:208:

TTGATTGTGA AATCAGGTAT TCAACAGAGA AATTTCTCAG CCTCCTAC 48

(2) INFORMATION FOR SEQ ID NO:209:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for prointerleukin 1 beta

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:209:

CTACTTCTGC TTTTGAAAGC TATAAAAACA GCGAGGGAGA AACTGGC 47

(2) INFORMATION FOR SEQ ID NO:210:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: human interleukin 2 receptor gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:210:

AGAAAGGATT CATAAATGAA GTTCAATCCT TCTCATCACC CCAGCCCA 48

(2) INFORMATION FOR SEQ ID NO:211:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human interleukin 2 receptor gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:211:

TTTGAAAAAT TACCGCAAAC TATATTGTCA TCAAAAAAAA AAAAAA 46

(2) INFORMATION FOR SEQ ID NO:212:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human interleukin 4 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:212:

ATCTGGTGTA ACGAAAATTT CCAATGTAAA CTCATTTTCC CTCGG 45

(2) INFORMATION FOR SEQ ID NO:213:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human interleukin 4 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:213:

GGTTTCAGCA ATTTTAAATC TATATATAGA GATATCTTTG TCAGCATT 48

(2) INFORMATION FOR SEQ ID NO:214:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human interleukin 5 (IL-5) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:214:

CATTTCCTCA AAGACAGACA ATAAATTGAC TGGGGACGCA GTCTTGTACT 50

(2) INFORMATION FOR SEQ ID NO:215:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human interleukin 7 (IL-7) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:215:

TTGCTTTGAT TCAGGCCAGC TGGTTTTTCT GCGGTGATTC GGAAATTCGC 50

(2) INFORMATION FOR SEQ ID NO:216:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human interleukin 9 gene (IL-9)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:216:

TTCCGTGTTT GAGAGGGAGC TTTAAATACC ACTCGATTTG AAGGTGTC 48

(2) INFORMATION FOR SEQ ID NO:217:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human int-1 mammary oncogene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:217:

ACTTCAGCCA GCGCCGCAAC TATAAGAGGC GGTGCCGCCC GCCGT 45

(2) INFORMATION FOR SEQ ID NO:218:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human jun-B gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:218:

TCCGTGGCTG ACTAGCGCGG TATAAAGGCG TGTGGCTCAG GCTGAG 46

(2) INFORMATION FOR SEQ ID NO:219:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human DNA for 65 kD keratin type II

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:219:

GCCCAACAAC CTCCTCAAAT GTATATAAAG GGATTTTTAT TGCACA 46

(2) INFORMATION FOR SEQ ID NO:220:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human ultra high-sulphur keratin protein gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:220:

TGGTGTGTTC CTATGTGGGA TATAAAGAGC CGGGGCTCAG GGGGCT 46

(2) INFORMATION FOR SEQ ID NO:221:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human alpha-lactalbumin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:221:

CCTGAGGCTT TCTGCATGAA TATAAATAAA TGAAACTGAG TGATGCT 47

(2) INFORMATION FOR SEQ ID NO:222:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human LAG-1 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:222:

GTCCTAGGCC TCAGAGTCCC TATAAGAGAG ATTCCCAACT CAGTA 45

(2) INFORMATION FOR SEQ ID NO:223:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human lecithin-cholesterol acyltransferase (LCAT) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:223:

CTGAGGCTGT GCCCCTTTCC GGCAATCTCT GGCCACAACC CCCACTGG 48

(2) INFORMATION FOR SEQ ID NO:224:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human lecthin-cholesterol acyltransferase (LCAT) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:224:

CCCCTCCCAC TCCCACACCA GATAAGGACA GCCCAGTGCC GCTTT 45

(2) INFORMATION FOR SEQ ID NO:225:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human lymphocyte-specific protein kinase (lck) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:225:

GGCAGCAGAT CTTGGGGGAG CCCCTTCAGC CCCCTCTTCC ATTCCCTCAG 50

(2) INFORMATION FOR SEQ ID NO:226:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human leukocyte fuction-associated antigen-1 (LFA-1) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:226:

GGGTATCTCA CTGTGGTTTG ATTTGCATTT CTCTAATGAC TAATAGTG 48

(2) INFORMATION FOR SEQ ID NO:227:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human leukocyte fuction-associated antigen-1 (LFA-1) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:227:

ATGTCTCTAA CTTGCTTACA CTTCCTCCCT GAACCCTGCG GTTTCA 46

(2) INFORMATION FOR SEQ ID NO:228:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human leukocyte function-associated antigen-1 (LFA-1) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:228:

TCCTGCAGGC ACACCTCCCT CCCCGCCTGC CAGTGTCACC AGCCTGTT 48

(2) INFORMATION FOR SEQ ID NO:229:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human leukocyte function-associated antigen-1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:229:

CTGTTGCCTC TGTGAGAAAG TACCACTGTA AGAGGCCAAA GGGCATGATC 50

(2) INFORMATION FOR SEQ ID NO:230:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: human lipoprotein lipase (LPL) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:230:

TATTTGCATA TTTCCAGTCA CATAAGCAGC CTTGGCGTGA AAACAGT 47

(2) INFORMATION FOR SEQ ID NO:231:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human leukocyte adhesion molecule-1 (LAM-1)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:231:

TGGGTTAGAG AAATGAAAGA AAGCAAGGCT TTCTGTTGAC ATTCAGTGCA 50

(2) INFORMATION FOR SEQ ID NO:232:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human lysozyme gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:232:

AGAAGGAAGT TAAAAGATGT TAAATACTGG GGCCAGCTCA CCCTGG 46

(2) INFORMATION FOR SEQ ID NO:233:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human mannose binding protein 1 (MBP1) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:233:

AGGCATGGGT CATCTATTTC TATATAGCCT GCACCCAGAT TGTAGG 46

(2) INFORMATION FOR SEQ ID NO:234:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human mast cell carboxypeptidase A (MC-CPA) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:234:

CATCAAGATA AGGGCTGAGG CATAAAACTG CCAGAGGGTC TCAAGG 46

(2) INFORMATION FOR SEQ ID NO:235:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human P-glycoprotein (MDR1) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:235:

CTTTGCCACA GGAAGCCTGA GCTCATTCGA GTAGCGGCTC TTCCA 45

(2) INFORMATION FOR SEQ ID NO:236:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human bone marrow serine protease gene (medullasin)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:236:

ACGGCCTCCC AGCACAGGGC TATAAGAGGA GCCGGGCGGG CACGG 45

(2) INFORMATION FOR SEQ ID NO:237:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human microsomal epoxide hydrolase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:237:

TTGCTGTGCA GAGTCCAGGG GAGATAACCA CGCTGTGCAC ACATGAG 47

(2) INFORMATION FOR SEQ ID NO:238:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 52 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human metallothionein-Ie gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:238:

GCAGCCAGTT GCAGGGCTCC ATTCTGCTTT CCAACTGCCT GACTGCTTGT TC 52

(2) INFORMATION FOR SEQ ID NO:239:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human myoglobin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:239:

TTGTCAAGCA TCCCAGAAGG TATAAAAACG CCCTTGGGAC CAGGCA 46

(2) INFORMATION FOR SEQ ID NO:240:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human melanoma growth stimulatory activity (MGSA) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:240:

GCTTTCCAGC CCCAACCATG CATAAAAGGG GTTCGCGGAT CTCGGAG 47

(2) INFORMATION FOR SEQ ID NO:241:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human alpha-MHC gene for myosin heavy chain (N-terminus)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:241:

AGAGGGTGGG GGAAACGGGA TATAAAGGAA CTGGAGCTTT GAGGAG 46

(2) INFORMATION FOR SEQ ID NO:242:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human class II invariant gamma-chain gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:242:

GATTCCTCTC CAGCACCGAC TTTAAGAGGC GAGCCGGGGG GTCAG 45

(2) INFORMATION FOR SEQ ID NO:243:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 41 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human motilin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:243:

CCCAGGGTTG GGAGGTATAT AAGAACCCGT CAGATCAGCC G 41

(2) INFORMATION FOR SEQ ID NO:244:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human myeloperoxidase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:244:

CCACCCCCAG CTTAGAGGAC ATAAAAGCGC AGATTGAGCT AAGAGGAGCT 50

(2) INFORMATION FOR SEQ ID NO:245:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human mitochondrial RNA-processing endoribonuclease RNA gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:245:

AAACACAATT TCTTTAGGGC TATAAAATAC TACTCTGTGA AGCTGAGGA 49

(2) INFORMATION FOR SEQ ID NO:246:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human myc-oncogene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:246:

GAGGGAGGGA TCGCGCTGAG TATAAAAGCC GGTTTTCGGG GCTTTAT 47

(2) INFORMATION FOR SEQ ID NO:247:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human Na,K-ATPase beta subunit (ATP1B) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:247:

GCACGGCCGC CGGGGCGCGG TATATAGTAA AGGTAGGGCG GGCGCA 46

(2) INFORMATION FOR SEQ ID NO:248:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human neuromedin K receptor

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:248:

GAAGCGTGGG ACCCCATGAG TATAAAGAGA GCCTGTAGCG CAGG 44

(2) INFORMATION FOR SEQ ID NO:249:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for heavy neurofiliment subunit (NF-H) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:249:

TTGGACCCGG CCGCGGCGGC TATAAAAGGG CCGGCGCCCT GGTCGT 46

(2) INFORMATION FOR SEQ ID NO:250:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human nuclear factor NF-IL6 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:250:

CGGTTGCTAC GGGCCGCCCT TATAAATAAC CGGGCTCAGG AGAAACT 47

(2) INFORMATION FOR SEQ ID NO:251:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human neurofilament subunit NF-L gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:251:

TGCGTCAGGA CCTCCCGGCG TATAAATAGG GGTGGCAGAA CGGCGC 46

(2) INFORMATION FOR SEQ ID NO:252:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human neurokinin-2 receptor (NK-2) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:252:

TCTCTTCAGC GAAGGGGTTG ATTTATAAGG GTGTTTTCTG CTCTGACA 48

(2) INFORMATION FOR SEQ ID NO:253:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human n-myc gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:253:

GGGTGTGTCA GATTTTTCAG TTAATAATAT CCCCCGAGCT TCAAAGCGC 49

(2) INFORMATION FOR SEQ ID NO:254:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human ornithine decarboxylase (ODC1) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:254:

CCATGGCGAC CCGCCGGTGC TATAAGTAGG GAGCGGCGTG CCGTGG 46

(2) INFORMATION FOR SEQ ID NO:255:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human ornithine transcarbamylase (OTC) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:255:

ATACACAGCG GTGGAGCTTG GCATAAAGTT CAAATGCTCC TACACC 46

(2) INFORMATION FOR SEQ ID NO:256:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human prepro-oxytocin-neurophysin I gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:256:

CTCCACCGAC GCAATGCCCA GGCATAAAAA GGCCAGGCCG AGAGACCGCC 50

(2) INFORMATION FOR SEQ ID NO:257:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cytochrome P450scc gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:257:

TATGGCCTTG AGCTGGTAGT TATAATCTTG GCCCTGGTGG CCCAG 45

(2) INFORMATION FOR SEQ ID NO:258:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human p53 gene for transmembrane related p53

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:258:

CCCCTCCCAT GTGCTCAAGA CTGGCGCTAA AAGTTTTGAG CTTCTCAAAA 50

(2) INFORMATION FOR SEQ ID NO:259:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human Alzheimer's disease amyloid A4 precursor gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:259:

GGGAGGCCTG CGGGGTCGGA TGATTCAAGC TCACGGGGAC GAGCAGG 47

(2) INFORMATION FOR SEQ ID NO:260:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 54 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human Alzheimer's disease amyloid A4 precursor gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:260:

CGGGGACGAG CAGGAGCGCT CTCGACTTTT CTAGAGCCTC AGCGTCCTAG GACT 54

(2) INFORMATION FOR SEQ ID NO:261:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human Alzheimer's disease amyloid A4 precursor

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:261:

GCGGGGTGGG CCGGATCAGC TGACTCGCCT GGCTCTGAGC CCCGCCGC 48

(2) INFORMATION FOR SEQ ID NO:262:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human Alzheimer's disease amyloid A4 precursor gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:262:

CCGCCGCCGC GCTCGGGCTC CGTCAGTTTC CTCGCCAGCG GTAGGCGAG 49

(2) INFORMATION FOR SEQ ID NO:263:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for plasminogen activator inhibitor 1 (PAI-1)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:263:

TATTTCCTGC CCACATCTGG TATAAAAGGA GGCAGTGGCC CACAGAG 47

(2) INFORMATION FOR SEQ ID NO:264:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human platelet-derived growth factor A-chain (PDGF) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:264:

AGGGGCGCGG CGGCGGCGGC TATAACCCTC TCCCCGCCGC CGGCC 45

(2) INFORMATION FOR SEQ ID NO:265:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human PGP9.5 gene for neuron-specific ubiquitin

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:265:

ACAGTGCGTC TGGCCGGCGC TTTATAGCTG CAGCCTGGCG CTCCGC 46

(2) INFORMATION FOR SEQ ID NO:266:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human plasminogen gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:266:

CTCCACCGAC GCAATGCCCA GGCATAAAAA GGCCAGGCCG AGAGACCGCC 50

(2) INFORMATION FOR SEQ ID NO:267:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human phenylethanolamine N-methylase (PNMT) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:267:

TCGGGGCGGG GGTCGGGCGG TAGAAAAAAG GGCCGCGAGG CGAGCGGGG 49

(2) INFORMATION FOR SEQ ID NO:268:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human opiomelanocortin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:268:

CTCCCCGTGT GCAGACGGTG ATATTTACCG CCAAATGCGA ACCAGGC 47

(2) INFORMATION FOR SEQ ID NO:269:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene PRB3L for proline-rich protein G1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:269:

GCCACTGTTC TGCTCCTCTT TATAAAGGGA GCTGCCATGG TTCTCC 46

(2) INFORMATION FOR SEQ ID NO:270:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human PRB4 gene for proline-rich protein Po

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:270:

CATTGTTTTG CTCCTCTTTA TAAAGGGAGT TGCCACGTTC CTCC 44

(2) INFORMATION FOR SEQ ID NO:271:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human prolactin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:271:

AGGCTTTGAT ATCAAAGGTT TATAAAGCCA ATATCTGGGA AAGAGA 46

(2) INFORMATION FOR SEQ ID NO:272:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human prothymosin-alpha gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:272:

CCGAGCGCCG CCCACTAATC TATATTAAAG CTTCTGGCGC CGCGTG 46

(2) INFORMATION FOR SEQ ID NO:273:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human protamine 2 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:273:

TCATAGTGGG CGTCCCCCTT TATATACAAG CTCCCGGGGA GCCTTG 46

(2) INFORMATION FOR SEQ ID NO:274:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human SPR2-1 gene for small proline rich protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:274:

CTGGGTGGGG TAGCAGGCTC TATAAAGAGA TCCTCTGCTG CACGAC 46

(2) INFORMATION FOR SEQ ID NO:275:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human estrogen-responsive gene pS2

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:275:

TAAGCAAACA GAGCCTGCCC TATAAAATCC GGGGCTCGGG CGGCCTC 47

(2) INFORMATION FOR SEQ ID NO:276:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human pulmonary surfactant apoprotein (PSAP) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:276:

AGCCTGGCAG CCCCCACATC TATAAATGCT GCGTCTACCT TACCCT 46

(2) INFORMATION FOR SEQ ID NO:277:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for prostatic secretory protein PSP-94

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:277:

TGCGTGGTTG CCCTCTCCAG TATAAAAGTT TGATGCAGCT TTTCC 45

(2) INFORMATION FOR SEQ ID NO:278:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human parathyroid hormone-related peptide (PTHRP) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:278:

GAGGTAGACA GACAGCTATG TATATATATG TGGGTTTCGC TACAAGTGG 49

(2) INFORMATION FOR SEQ ID NO:279:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for purine nucleoside phosphorylase

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:279:

CTGGGGACTC CAGGGCAAGG GATATAAGCC AGAGCCTAGA CCAGTG 46

(2) INFORMATION FOR SEQ ID NO:280:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human rDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:280:

ATTTTGGGCC GCCGGGTTAT 20

(2) INFORMATION FOR SEQ ID NO:281:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human regenerating protein (reg) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:281:

GTTCTTATCT CAGATCCTGA TATAAAGCTC CTACAGCTAC CTGGCC 46

(2) INFORMATION FOR SEQ ID NO:282:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human renin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:282:

ATCACCCCAT GCATGGAGTG TATAAAAGGG GAAGGGCTAA GGGAGCC 47

(2) INFORMATION FOR SEQ ID NO:283:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene fragment for retinol binding protein (RBP)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:283:

CGACCCCCTC CCCCCGGCGC TATAAAGCAG CGGGGCGGCC GCGGCG 46

(2) INFORMATION FOR SEQ ID NO:284:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human serum amyloid A (GSAA1) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:284:

CACCCCGCTA ATTTAAAAAA TATATATACA GATATATAGT GGAGATGG 48

(2) INFORMATION FOR SEQ ID NO:285:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human SAA1 beta gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:285:

AACCAGCAGG GAAGGCTCAG TATAAATAGC AGCCACCGCT CCCTGGC 47

(2) INFORMATION FOR SEQ ID NO:286:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene fragment for HLA class II SB 4-beta chain

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:286:

CTACTTGGGT TCATGGTCTC TAATATTTCA AACAGGAGCT CCCTTTAG 48

(2) INFORMATION FOR SEQ ID NO:287:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human c-sis proto-oncogene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:287:

TCGCACTCTC CCTTCTCCTT TATAAAGGCC GGAACAGCTG AAAGGG 46

(2) INFORMATION FOR SEQ ID NO:288:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human SLPI gene for secretory leukocyte protease inhibitor

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:288:

CACACCCACT GGTGAAAGAA TAAATAGTGA GGTTTGGCAT TGGCCA 46

(2) INFORMATION FOR SEQ ID NO:289:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human superoxide dismutase (SOD-1) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:289:

CGAGGCGCGG AGGTCTGGCC TATAAAGTAG TCGCGGAGAC GGGGTG 46

(2) INFORMATION FOR SEQ ID NO:290:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human ornithine decarboxylase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:290:

TCCATGGCGA CCCGCCGGTG CTATAAGTAG GGAGCGGCGT GCCGT 45

(2) INFORMATION FOR SEQ ID NO:291:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human steroid 5-alpha-reductase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:291:

CTGCCCCCGC GCCGCCGCCC TATATGTTGC CCGCCGCGGC CTCTG 45

(2) INFORMATION FOR SEQ ID NO:292:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human substance P receptor gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:292:

GTGACGTCTC TGCAGGGGGT TATAAAAGCC TCGTGCGCAG CTAA 44

(2) INFORMATION FOR SEQ ID NO:293:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human synaptobrevin 1 (SYB1) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:293:

CCGGGAGGCG TGGTCAGCAC TAATAAAGGC GGAGGCCGGC GCGGCA 46

(2) INFORMATION FOR SEQ ID NO:294:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human tyrosine aminotransferase (TAT) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:294:

CAACGCCCAT TTGTGGAGAC TATTTCAGGA GTTAGGATTT GCATCTG 47

(2) INFORMATION FOR SEQ ID NO:295:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human T-cell receptor V-beta gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:295:

GACAGATGCA TTCTGTGGGG ATAAAATGTC ACAAAATTCA TTTCTTT 47

(2) INFORMATION FOR SEQ ID NO:296:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human T-cell receptor V-beta gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:296:

TCACAGAGGG CCTGGTCTAG AATATTCCAC ATCTGCTCTC ACTCT 45

(2) INFORMATION FOR SEQ ID NO:297:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human T-cell receptor V-beta gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:297:

GACAGATGCA TTCTGTGGGG ATAAAATGTC ACAAAATTCA TTTCTTT 47

(2) INFORMATION FOR SEQ ID NO:298:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human T-cell receptor V-beta gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:298:

TCACAGAGGG CCTGGTCTGG AATATTCCAC ATCTGCTCTC ACTCTG 46

(2) INFORMATION FOR SEQ ID NO:299:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human T-cell receptor V-beta chain gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:299:

TGTTACTGTA GGAACTACCG TATAAGGACA GGATGTCCCA CCTCC 45

(2) INFORMATION FOR SEQ ID NO:300:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human transferrin (Tf) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:300:

CCGCCCAGGC CGGGAATGGA ATAAAGGGAC GCGGGGCGCC GGAGG 45

(2) INFORMATION FOR SEQ ID NO:301:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human interleukin 3 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:301:

GGGCACCTTG 10

(2) INFORMATION FOR SEQ ID NO:302:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human tissue factor gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:302:

CGGGAGAGCG CGCCGCCGGC CCTTTATAGC GCGCGGGGCA CCGGCTCCCC 50

(2) INFORMATION FOR SEQ ID NO:303:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human transforming growth factor-beta (TGF-beta)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:303:

TGCCTTGCCC ATGGGGGCTG TATTTAAGGA CACCGTGCCC CAAGCCC 47

(2) INFORMATION FOR SEQ ID NO:304:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human transforming growth factor beta-3 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:304:

GAGACGTCAT GGGAGGGAGG TATAAAATTT CAGCAGAGAG AAATAGA 47

(2) INFORMATION FOR SEQ ID NO:305:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human transforming growth factor beta-2 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:305:

CACGTGGTTC AGAGAGAACT TATAAATCTC CCCTCCCCGC GAAGA 45

(2) INFORMATION FOR SEQ ID NO:306:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human tyrosine hydroxylase (TH) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:306:

GGCTTTGACG TCAGCTCAGC TTATAAGAGG CTGCTGGGCC AGGGCT 46

(2) INFORMATION FOR SEQ ID NO:307:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human metallothionein gene IIA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:307:

TCGTCCCGGC TCTTTCTAGC TATAAACACT GCTTGCCGCG CTGCAC 46

(2) INFORMATION FOR SEQ ID NO:305:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human thrombospondin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:308:

CCCAGGAATG CGAGCGCCCC TTTAAAAGCG CGCGGCTCCT CCGCCT 46

(2) INFORMATION FOR SEQ ID NO:309:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human thyroxine-binding globulin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:309:

ATAATGTTGC TATAACATCT GAATGACAGT CCATGGCATT ATTTC 45

(2) INFORMATION FOR SEQ ID NO:310:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human thyroglobulin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:310:

GAAAGTGCCA ACGGCAGCTC TATAAAAGCT CCCTGGCCAG GGGACCT 47

(2) INFORMATION FOR SEQ ID NO:311:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for tumor necrosis factor (TNF-alpha)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:311:

CTCCTCTCGC CCCAGGGACA TATAAAGGCA GTTGTTGGCA CACCCA 46

(2) INFORMATION FOR SEQ ID NO:312:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human lymphotoxin (TNF-beta) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:312:

GCTGCCACTG CCGCTTCCTC TATAAAGGGA CCTGAGCGTC CGGGCC 46

(2) INFORMATION FOR SEQ ID NO:313:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human type I DNA topoisomerase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:313:

TGACGTCGCC GACGTGTTGT TTAAAAGCGG GCGCGCAGGC GCAGTGAGCC 50

(2) INFORMATION FOR SEQ ID NO:314:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human triosephosphate isomerase (TPI) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:314:

AGTTCCACTT CGCGGCGCTC TATATAAGTG GGCAGTGGCC GGACTGC 47

(2) INFORMATION FOR SEQ ID NO:315:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human thyroid peroxidase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:315:

ATCCAAGCGC AGAGTCAGTT TATAAGGTGG GTAACCAAGT CCCT 44

(2) INFORMATION FOR SEQ ID NO:316:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human transferrin receptor gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:316:

GGCCGGGGGC GGGGCCAGGC TATAAACCGC CGGTTAGGGG CCGCCA 46

(2) INFORMATION FOR SEQ ID NO:317:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human tryptase -I gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:317:

CGCCCCCTCC TGATCTGGAA GGATAAATGG GGAGGGGAGA GCCACTGGGT 50

(2) INFORMATION FOR SEQ ID NO:318:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human beta 2 gene for beta-tubulin

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:318:

GCGGAGGCGG GCAGGGAGGG TATATAAGCG TTGGCGGACG GTCGGT 46

(2) INFORMATION FOR SEQ ID NO:319:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for U 6 RNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:319:

GTATTTCGAT TTCTTGGCTT TATATATCTT GTGGAAAGGA CGAAAC 46

(2) INFOPMATION FOR SEQ ID NO:320:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human uPA gene for
urokinase-plasminogen activator

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:320:

GGCGGCGCCG GGGCGGGCCC TGATATAGAG CAGGCGCCGC GGGTCGC 47

(2) INFORMATION FOR SEQ ID NO:321:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human proto-oncogene vav

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:321:

GCAGGCGTGC GGGCGGGTGG GTGGTGGAGG CTGCGA 36

(2) INFORMATION FOR SEQ ID NO:322:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human vascular cell adhesion molecule-1 (VCAM1) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:322:

GCCTCTGCAA CAAGACCCTT TATAAAGCAC AGACTTTCTA TTTCA 45

(2) INFORMATION FOR SEQ ID NO:323:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human vimentin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:323:

ACCCTCTTTC CTAACGGGGT TATAAAAACA GCGCCCTCGG CGGGG 45

(2) INFORMATION FOR SEQ ID NO:324:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human U1 RNA gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:324:

GTAAAGGGTG AGGTATATGG AGCTGTGACA GGGCAGAAGT GTGTGAAGTC 50

(2) INFORMATION FOR SEQ ID NO:325:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for small nuclear U1 RNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:325:

GTAAAGAGTG AGGCGTATGA GGCTGTGTCG GGGCAGAGGC CCAAGATCTC 50

(2) INFORMATION FOR SEQ ID NO:326:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human small nuclear U2 RNA gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:326:

TTGAATGTGG ATGAGAGTGG GACGGTGACG GCGGGCGCGA AGGCGAGCGC 50

(2) INFORMATION FOR SEQ ID NO:327:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human U3 small nuclear RNA gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:327:

AAAAGTTTGC GGCAGATGTA GACCTAGCAG AGGTGTGCGA GGAGGCCGTT 50

(2) INFORMATION FOR SEQ ID NO:328:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human U4C small nuclear RNA gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:328:

AAATGGTAGT CATCATCCGT GGGGGAGCGG GGCGCGAATA AAGCCTTTCC 50

(2) INFORMATION FOR SEQ ID NO:329:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human histone H3.3 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:329:

GGGCGGGGCG GCGTGTGTTG GGGGATAGCC TCGGTGTCAG CCATCTTTCA 50

(2) INFORMATION FOR SEQ ID NO:330:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human histone H4 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:330:

AGTTCGGTCC GCCAACTGTC GTATAAAGGC GCTGCCTCAG GTCAGAGGCC 50

(2) INFORMATION FOR SEQ ID NO:331:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human non-histone chromosomal protein HMG-14 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:331:

TGGGGGGCGG CCCGGCCGGC GGGGAGGGGG AGCCGCGGCC GGGACGCGGG 50

(2) INFORMATION FOR SEQ ID NO:332:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human ribosomal protein S14 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:332:

AAGTAATAAA CCGTCTTTCC TTATGACGAG TCTTAAACTC TTTGGGAGGA 50

(2) INFORMATION FOR SEQ ID NO:333:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for alpha tubulin (b alpha 1)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:333:

CGCGACCGAG GGTCTGGGCG TCCCGGCTGG GCCCCGTGTC TGTGCGCACG 50

(2) INFORMATION FOR SEQ ID NO:334:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human skeletal alpha-actin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:334:

AGGGAATCGC CCGCGGGCTA TATAAAACCT GAGCAGAGGG ACAAGCGGCC 50

(2) INFORMATION FOR SEQ ID NO:335:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human epidermal 67-kDa Keratin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:335:

GGAAGATCTT GTGTGATAAA ACAATTACCA CATGAACCAA TCTTGCATGC 50

(2) INFORMATION FOR SEQ ID NO:336:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human 50 KDatype I epidermal keratin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:336:

GACCCGCCCC CTACCCATGA GTATAAAGCA CTCGCATCCC TTTGCAATTT 50

(2) INFORMATION FOR SEQ ID NO:337:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human alpha-1 collagen type I gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:337:

CTGCTCTCCA TCAGGACAGT ATAAAAGGGG CCCGGGCCAG TCGTCGGAGC 50

(2) INFORMATION FOR SEQ ID NO:338:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human collagen type-III gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:338:

GTGAGGGAAG CCAAACTTTT TCCTATTTAA GGCCAAAGCA AAGGAATCTC 50

(2) INFORMATION FOR SEQ ID NO:339:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human pro-alpha-2 (I) mRNA for collagen N-prepropeptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:339:

CAGGGAAACT TTTGCCGTAT AAATAGGGCA GATCCGGGAT TTGTTATTTT 50

(2) INFORMATION FOR SEQ ID NO:340:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human fibronectin (FN) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:340:

TCCAGAGGGG CGGGAGGGCC GTCCCATATA AGCCCGGCTC CCGCGCTCCG 50

(2) INFORMATION FOR SEQ ID NO:341:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human von Willebrand factor gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:341:

TGTTTCCTTT TGGTAATTAA AAGGAGGCCA ATCCCCTGTT GTGGCAGCTC 50

(2) INFORMATION FOR SEQ ID NO:342:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for fibrinogen gamma chain

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:342:

TGGCTATCCC AGGAGCTTAC ATAAAGGGAC AATTGGAGCC TGAGA 45

(2) INFORMATION FOR SEQ ID NO:343:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for fibrinogen gamma chain

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:343:

CAGTCCTGGC TATCCCAGGA GCTTACATAA AGGGACAATT GGAGCCTGAG 50

(2) INFORMATION FOR SEQ ID NO:344:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human involucrin mRNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:344:

AGGCCAGGCT GCAGAATGAT ATAAAGAGTG CCCTGACTCC TGCTCAGCTC 50

(2) INFORMATION FOR SEQ ID NO:345:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human apolipoprotein A-I and C-III genes

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:345:

CCAGACCCTG GCTGCAGACA TAAATAGGCC CTGCAAGAGC TGGCTGCTTA 50

(2) INFORMATION FOR SEQ ID NO:346:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human apolipoprotein B-100 (apoB) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:346:

GCTCTTGCAG CCTGGGCTTC CTATAAATGG GGTGCGGGCG CCGGCCGCGC 50

(2) INFORMATION FOR SEQ ID NO:347:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human apolipoprotein A-I and C-III genes

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:347:

TCTAGGGATG AACTGAGCAG 20

(2) INFORMATION FOR SEQ ID NO:348:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Humanapolipoprotein A-I and C-III genes

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:348:

ACAGGCAGGA GGGTTCTGAC CTGTTTTATA TCATCTCCAG GGCAGCAGGC A 51

(2) INFORMATION FOR SEQ ID NO:349:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human albumin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:349:

TACAATTATT GGTTAAAGAA GTATATTAGT GCTAATTTCC CTCCGTTTGT 50

(2) INFORMATION FOR SEQ ID NO:350:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human albumin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:350:

TACAATTATT GGTTAAAGAA GTATATTAGT GCTAATTTCC CTCCGTTTGT C 51

(2) INFORMATION FOR SEQ ID NO:351:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human serum prealbumin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:351:

CCTAGCTCAG GAGAAGTGAG TATAAAAGCC CCAGGCTGGG AGCAGCCATC 50

(2) INFORMATION FOR SEQ ID NO:352:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human alpha-fetoprotein (AFP) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:352:

TAACAGGCAT TGCCTGAAAA GAGTATAAAA GAATTTCAGC ATGATTTTCC 50

(2) INFORMATION FOR SEQ ID NO:353:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 41 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human C-reactive protein gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:353:

AGGCAGGAGG AGGTAGCTCT AAGGCAAGAG ATCTGGGACT T 41

(2) INFORMATION FOR SEQ ID NO:354:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene A for alpha 1-acid glycoprotein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:354:

AAGTGACCGC CCATAGTTTA TTATAAAGGT GACTGCACCC TGCAGCCACC 50

(2) INFORMATION FOR SEQ ID NO:355:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene A for alpha 1-acid glycoprotein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:355:

AAGTGACCGC CCATAGTTTA TTATAAAGGT GACTGCACCC TGCAGCCACC A 51

(2) INFORMATION FOR SEQ ID NO:356:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for L apoferritin

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:356:

CGGCGCACCA TAAAAGAAGC CGCCCTAGCC ACGTCCCCTC 40

(2) INFORMATION FOR SEQ ID NO:357:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 41 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for L apoferritin

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:357:

CGGCGCACCA TAAAAGAAGC CGCCCTAGCC ACGTCCCCTC G 41

(2) INFORMATION FOR SEQ ID NO:358:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Olive baboon alpha-1 globin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:358:

GGCGTGCCCC CGCGCCCGGA GCATAAACCC TGGCGCGCTC GCGGCCCGGC 50

(2) INFORMATION FOR SEQ ID NO:359:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Olive baboon alpha-1 globin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:359:

GGCGTGCCCC CGCGCCCGGA GCATAAACCC TGGCGCGCTC GCGGCCCGGC A 51

(2) INFORMATION FOR SEQ ID NO:360:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human alpha-globin germ line gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:360:

GTGCCAACAA TGGAGGTGTT TACCTGTCTC AGACCAAGGA CCTCTCTGCA 50

(2) INFORMATION FOR SEQ ID NO:361:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Chimpanzee gene for alpha-like zeta-1-globin

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:361:

CCTGGCTGGG CCCAGCTCCC TGTATATAAG GGGACCCTGG GGGCTGAGCA 50

(2) INFORMATION FOR SEQ ID NO:362:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Chimpanzee gene for alpha-like zeta-1-globin

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:362:

CCTGGCTGGG CCCAGCTCCC TGTATATAAG GGGACCCTGG GGGCTGAGCA C 51

(2) INFORMATION FOR SEQ ID NO:363:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human alpha globin gene cluster on chromosome 16: zeta gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:363:

CTGGCTGGGC CCAGCTCCCT GTATATAAGG GGACCCTGGG GGCTGAGCAC 50

(2) INFORMATION FOR SEQ ID NO:364:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human theta 1-globin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:364:

CCGCGGGACC CCTGGCCGGT CCGCGCAGGC GCAGCGGGGT CGCAGGGCGC 50

(2) INFORMATION FOR SEQ ID NO:365:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Macaque cynomolgus beta-globin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:365:

GCAGGAGCCA GGGCTGGGCA TAAAAGTCAG GGCAGAGCCA TCTATTGCTT 50

(2) INFORMATION FOR SEQ ID NO:366:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Chimpanzee beta-globin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:366:

GCAGAAGCCA GGGCTGGGCA TAAAAGTCAG GGCAGAGCCA TCTATTGCTT 50

(2) INFORMATION FOR SEQ ID NO:367:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human germ line gene for beta-globin

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:367:

GCAGGAGCCA GGGCTGGGCA TAAAAGTCAG GGCAGAGCCA TCTATTGCTT 50

(2) INFORMATION FOR SEQ ID NO:368:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Spider monkey (A.geoffroyi)
delta-globin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:368:

CAGGGAGAAC AGGACCAGCA TAAAAGGCAG GGCAGGGCTA ACTGTTGCTT 50

(2) INFORMATION FOR SEQ ID NO:369:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human transferrin receptor gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:369:

GGGCGGGGCC AGGCTATAAA CCGCCGGTTA GGGGCCGCCA TCCCCTCAGA 50

(2) INFORMATION FOR SEQ ID NO:370:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human beta-2-adrenergic receptor gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:370:

AGTTCCCCTA AAGTCCTGTG CACATAACGG GCAGAACGCA CTGCGAAGCG 50

(2) INFORMATION FOR SEQ ID NO:371:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human IgE receptor gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:371:

GGTGGCAAGC CCATATTTAG GTCTATGAAA ATAGAAGCTG TCAGTGGCTC 50

(2) INFORMATION FOR SEQ ID NO:372:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human oncogene c-fos

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:372:

TTCATAAAAC GCTTGTTATA AAAGCAGTGG CTGCGGCGCC TCGTACTCCA 50

(2) INFORMATION FOR SEQ ID NO:373:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human c-myc oncogene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:373:

AATCTCCGCC CACCGGCCCT TTATAATGCG AGGGTCTGGA CGGCTGAGGA 50

(2) INFORMATION FOR SEQ ID NO:374:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human B-cell leukemia/lymphoma 2 (bcl-2) proto-oncogene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:374:

CCGCCCCTCC GCGCCGCCTG CCCGCCCGCC CGCCGCGCTC CCGCCCGCCG 50

(2) INFORMATION FOR SEQ ID NO:375:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human p53 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:375:

ACTCCATTTC CTTTGCTTCC TCCGGCAGGC GGATTACTTG CCCTTACTTG 50

(2) INFORMATION FOR SEQ ID NO:376:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene homologous to bladder carcinoma oncogene T24

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:376:

CGCGGCCCTA CTGGCTCCGC CTCCCGCGTT GCTCCCGGAA GCCCCGCCCG 50

(2) INFORMATION FOR SEQ ID NO:377:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human c-abl gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:377:

GGGGCGGGCC TGGCGGGCGC CCTCTCCGGG CCCTTTGTTA ACAGGCGCGT 50

(2) INFORMATION FOR SEQ ID NO:378:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human metallothionein-i-a gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:378:

CGGCCCTCTT TCCCCTGACC ATAAAAGCAG CCGCTGGCTG CTGGGCCCTA 50

(2) INFORMATION FOR SEQ ID NO:379:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human metallothinonein I-B gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:379:

ACCCCACCAC CTCCCCCGAC TATAAAGGAG CAGCCAGCTC CTGGGCTCCA 50

(2) INFORMATION FOR SEQ ID NO:380:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human metallothionein-If (MT-IF) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:380:

CCCGGCCCCC TCCCCTGACT ATCAAAGCAG CGGCCGGCTG TTTGGGTCCA 50

(2) INFORMATION FOR SEQ ID NO:381:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for 27 Kda heat shock protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:381:

CCCTCAAACG GGTCATTGCC ATTAATAGAG ACCTCAAACA CCGCCTGCTA 50

(2) INFORMATION FOR SEQ ID NO:382:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human 70 kDa heat shock protein gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:382:

GCGGGTCTCC GTGACGACTT ATAAAACCCC AGGGGCAAGC GGTCCGGATA 50

(2) INFORMATION FOR SEQ ID NO:383:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human macrophage alpha1-antitrypsin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:383:

TGCCTCCACC CGAAGTCTAC TTCCTGGGTG GGCAGGAACT GGGCACTGTG 50

(2) INFORMATION FOR SEQ ID NO:384:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human alpha1-antitrypsin (S variant) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:384:

CGTTGCCCCT CTGGATCCAC TGCTTAAATA CGGACGAGGA CAGGGCCCTG 50

(2) INFORMATION FOR SEQ ID NO:385:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human S variable segment 5'of antithrombin III gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:385:

TCTGCCCCAC CCTGTCCTCT GGAACCTCTG CGAGATTTAG AGGAAAGAAC 50

(2) INFORMATION FOR SEQ ID NO:386:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human pulmonary surfactant protein (SP5) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:386:

CCCCTCTCCC TACGGACACA TATAAGACCC TGGTCACACC TGGGAGAGGA 50

(2) INFORMATION FOR SEQ ID NO:387:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human Immunoglobulin kappa L-chain V region gene (HK122)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:387:

CCCCCTGCCC TGAAGACTTT TTATAGGCTG GTCACACCCG GAGCAGGAGT 50

(2) INFORMATION FOR SEQ ID NO:388:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human T cell receptor V-alpha/J-alpha chain (rearranged)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:388:

TTAAGGTTTG AATCCTCAGT GAACCAGGGC AGAAAAGAAT GATGAAATCC 50

(2) INFORMATION FOR SEQ ID NO:389:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for HLA-DR alpha heavy chain (class II antigen)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:389:

TGCATTTTAA TGGTCAGACT CTATTACACC CCACATTCTC TTTTCTTTTA 50

(2) INFORMATION FOR SEQ ID NO:390:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human MHC class IIHLA-DC-3-beta gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:390:

CTACCACGCA TGGAAACATC CACAGATTTT TATTCTTTCT GCCAGGTACA 50

(2) INFORMATION FOR SEQ ID NO:391:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human T-cell receptor CD3-gamma gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:391:

GCCTTCTCTC AAAGGCCCCA GCCCCAACAG TGATGGGTGG AGCCAGTCTA 50

(2) INFORMATION FOR SEQ ID NO:392:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human pregnancy-specific beta-1 glycoprotein mRNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:392:

CTGCCCTGGG AAGAGGCTCA GCACAGAAAG AGGAAGGACA GCACAGCTGA 50

(2) INFORMATION FOR SEQ ID NO:393:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human pregnancy-specific beta-1-glycoprotein 5 (PSG5)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:393:

AGAGAGGAGG GGACAGAGAG GTGTCCTGGG CCTGACCCCA CCCATGAGCC 50

(2) INFORMATION FOR SEQ ID NO:394:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human factor VIII gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:394:

CCTGTGGCTG CTTCCCACTG ATAAAAAGGA AGCAATCCTA TCGGTTACTG 50

(2) INFORMATION FOR SEQ ID NO:395:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human ubiquitin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:395:

TGACGCAACA CTCGTTGCAT AAATTTGCCT CCGCCAGCCC GGAGCATTTA 50

(2) INFORMATION FOR SEQ ID NO:396:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human proliferating cell nucleolar protein P120 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:396:

ACTATAATAC GCCAAGCGTG CGTTCTGCCG TTCCCTCCGA CACGCGCGAC 50

(2) INFORMATION FOR SEQ ID NO:397:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for delta-globin

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:397:

CAGGGAGGAC AGGACCAGCA TAAAAGGCAG GGCAGAGTCG ACTGTTGCTT 50

(2) INFORMATION FOR SEQ ID NO:398:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Gorilla fetal A-gamma-globin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:398:

CGGCTGGCTA GGGATGAAGA ATAAAAGGAA GCACCCTCCA GCAGTTCCAC 50

(2) INFORMATION FOR SEQ ID NO:399:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for fetal A-gamma and G-gamma hemoglobin

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:399:

CGGCTGGCTA GGGATGAAGA ATAAAAGGAA GCACCCTTCA GCAGTTCCAC 50

(2) INFORMATION FOR SEQ ID NO:400:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Orangutan epsilon-globin gene with flanking Alu repeats

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:400:

CAGAACTTCG GCAGTGAAGA ATAAAAGGCC ACACAGAGAG GCAGCAGCAC 50

(2) INFORMATION FOR SEQ ID NO:401:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human haptoglobin (Hp1) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:401:

TAAAAAGACC AGCAGATGCC CCACAGCACT GCTCTTCCAG AGGCAAGACC 50

(2) INFORMATION FOR SEQ ID NO:402:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 71 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human low molecular weight oligoadenylate synthetase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:402:

AAGACAGCTC CTCCCTTCTG AGGAAACGAA ACCAACAGCA GTCCAAGCTC AGTCAGCAGA 60

AGAGATAAAA G 71

(2) INFORMATION FOR SEQ ID NO:403:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene fragment for dihydrofolate reductase

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:403:

GGGGGGCGGG GCCTCGCCTG CACAAATAGG GACGAGGGGG CGGGGCGGCC 50

(2) INFORMATION FOR SEQ ID NO:404:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: Human thymidine kinase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:404:

GGCTCGTGAT TGGCCAGCAC GCCGTGGTTT AAAGCGGTCG GCGCGGGACC 50

(2) INFORMATION FOR SEQ ID NO:405:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human adenosine deaminase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:405:

GCGGGAGGCG GGGCCCGGCC CGTTAAGAAG AGCGTGGCCG GCCGCGGCC 49

(2) INFORMATION FOR SEQ ID NO:406:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human argininosuccinate synthase

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:406:

TGCCCCCGGG CCCTGTGCTT ATAACCTGGG ATGGGCACCC CTGCCAGTCC 50

(2) INFORMATION FOR SEQ ID NO:407:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human ornithine aminotransferase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:407:

GGGGGCGGGG CAGAATCAGC CTTTAAGTTG CAGTGACGCT CCGGCGTCAC 50

(2) INFORMATION FOR SEQ ID NO:408:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human tyrosine hydroxylase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:408:

TGACGTCAGC TCAGCTTATA AGAGGCTGCT GGGCCAGGGC TGTGG 45

(2) INFORMATION FOR SEQ ID NO:409:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human HMG CoA reductase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:409:

CAGCTCCGAG CGTGCGTAAG GTGAGGGCTC CTTCCGCTCC GCGACTGCGT 50

(2) INFORMATION FOR SEQ ID NO:410:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for lecithin-cholesterol acyltransferase

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:410:

CCTAGGGCCC CTCCCACTCC CACACCAGAT AAGGACAGCC CAGTGCCGCT 50

(2) INFORMATION FOR SEQ ID NO:411:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human porphobilinogen deaminase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:411:

CGCCCAGAGG GAGGGACCTC CCCTTCGAGG GAGGGCGCCG GAAGTGACGC 50

(2) INFORMATION FOR SEQ ID NO:412:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human porphobilinogen deaminasegene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:412:

GCACAGCACT CCCACTGACA ACTGCCTTGG TCAAGGTGGG CTTCAGGGCT 50

(2) INFORMATION FOR SEQ ID NO:413:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human URO-D gene for uroporphyrinogen decarboxylase

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:413:

GGGGGGCAGG CTCAGATTCA GGTTAAATTG TGGATTGAGC TCGCAGTTAC 50

(2) INFORMATION FOR SEQ ID NO:414:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human URO-D gene for uroporphyrinogen decarboxylase

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:414:

GGGGGGCAGG CTCAGATTCA GGTTAAATTG TGGATTGAGC TCGCAGTTAC A 51

(2) INFORMATION FOR SEQ ID NO:415:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human aldolase B (ALDOB) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:415:

AAAAAAAAAA CATGATGAGA AGTCTATAAA AATTGTGTGC TACCAAAGAT 50

(2) INFORMATION FOR SEQ ID NO:416:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human aldolase A gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:416:

GGTGGCGCTG CTCACCACAC ACAAGTGTTA TAGGAGGAGT CTGGCCCTTG 50

(2) INFORMATION FOR SEQ ID NO:417:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human aldolase A gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:417:

GGTGGCGCTG CTCACCACAC ACAAGTGTTA TAGGAGGAGT CTGGCCCTTG A 51

(2) INFORMATION FOR SEQ ID NO:418:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human aldolase A gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:418:

TGTGGGGCGG GCAGGAGCTG CCTTATAACC AGCCCGGGAA CCCCTAGCTC 50

(2) INFORMATION FOR SEQ ID NO:419:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human aldolase A gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:419:

TGTGGGGCGG GCAGGAGCTG CCTTATAACC AGCCCGGGAA CCCCTAGCTC A 51

(2) INFORMATION FOR SEQ ID NO:420:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human aldolase A gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:420:

GCTCGGCGGA GGGCGGAGTG GTGCCTTTAA AAGGCCGGGC GCCGCCTTCC 50

(2) INFORMATION FOR SEQ ID NO:421:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human aldolase A gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:421:

GCTCGGCGGA GGGCGGAGTG GTGCCTTTAA AAGGCCGGGC GCCGCCTTCC G 51

(2) INFORMATION FOR SEQ ID NO:422:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human aldolase A gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:422:

GCTAAATCGG CTGCGTTCCT CTCGGAACGC GCCGCAGAAG GGGTCCTGGT 50

(2) INFORMATION FOR SEQ ID NO:423:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human aldolase A gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:423:

GCTAAATCGG CTGCGTTCCT CTCGGAACGC GCCGCAGAAG GGGTCCTGGT G 51

(2) INFORMATION FOR SEQ ID NO:424:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human phosphoglycerate kinase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:424:

GAGGCGGGGT GTGGGGCGGT AGTGTGGGCC CTGTTCCTGC CCGCGCGGTG 50

(2) INFORMATION FOR SEQ ID NO:425:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for glucose 6-phosphate dehydrogenase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:425:

CAGGCGCCCG CCCCCGCCCC CGCCGATTAA ATGGGCCGGC GCGGCTCAGC 50

(2) INFORMATION FOR SEQ ID NO:426:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human hepatic lipase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:426:

GCAGTCTTCC CTAACAAAGT ATCTAATAGG CATTGTGGTC TCTTTGGCTT 50

(2) INFORMATION FOR SEQ ID NO:427:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human hepatic lipase mRNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:427:

GCAGTCTTCC CTAACAAAGT ATCTAATAGG CATTGTGGTC TCTTTGGCTT C 51

(2) INFORMATION FOR SEQ ID NO:428:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human protein C gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:428:

AGTGCTGAGG GCCAAGCAAA TATTTGTGGT TATGGATTAA CTCGAACTCC 50

(2) INFORMATION FOR SEQ ID NO:429:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human factor IX gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:429:

CCAGAAGTAA ATACAGCTCA GCTTGTACTT TGGTACAACT AATCGACCTT 50

(2) INFORMATION FOR SEQ ID NO:430:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human MHC III HLA factor B gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:430:

GCAGGTGCCA GAACACAGAT TGTATAAAAG GCTGGGGGCT GGTGGGGAGC 50

(2) INFORMATION FOR SEQ ID NO:431:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human pepsinogen gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:431:

CGATAAGGCG GGACCCAACT TGTATATAAG GGCAGCTCAT GCTGCTGCTC 50

(2) INFORMATION FOR SEQ ID NO:432:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human pepsinogen C gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:432:

CGATTAGACT AATCTTGGGC GTATAAAAGA GGAAAGAGTG CCCAGGTCTT 50

(2) INFORMATION FOR SEQ ID NO:433:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human collagenase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:433:

CTGGAAGGGC AAGGACTCTA TATATACAGA GGGAGCTTCC TAGCTGGGAT 50

(2) INFORMATION FOR SEQ ID NO:434:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human stromelysin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:434:

CCAAACAAAC ACTGTCACTC TTTAAAAGCT GCGCTCCCGA GGTTGGACCT 50

(2) INFORMATION FOR SEQ ID NO:435:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human alpha-amylase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:435:

TCTGATCCGT GCAGGGTATT AATGTGTCAG GGCTGAGTGT TCTGAGATTT 50

(2) INFORMATION FOR SEQ ID NO:436:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human pancreatic alpha-amylase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:436:

TGTAAAATGT GCTTCTTACA GGAATATAAA TAGTTTCTGG AAAGGACACT 50

(2) INFORMATION FOR SEQ ID NO:437:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human pancreatic amylase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:437:

TGTAAAATGT GCTTCTTACA GGAATATAAA TAGTTTCTGG AAAGGACACT 50

(2) INFORMATION FOR SEQ ID NO:438:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: human cytochrome P450c gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:438:

GCCACACGTA CAAGCCCGCC TATAAAGGTG GCAGTGCCTT CACCCTCACC 50

(2) INFORMATION FOR SEQ ID NO:439:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cytochrome P-450c gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:439:

GCCACACGTA CAAGCCCGCC TATAAAGGTG GCAGTGCCTT CACCCTCACC C 51

(2) INFORMATION FOR SEQ ID NO:440:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for cytochrome P(1)-450

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:440:

CACGTACAAG CCCGCCTATA AAGGTGGCAG TGCCTTCACC 40

(2) INFORMATION FOR SEQ ID NO:441:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human steroid 21-hydroxylase [P450 (C21)] B gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:441:

GGATGGCTGG GGCTCTTGAG CTATAAGTGG CACCTCAGGG CCCTGACGGG 50

(2) INFORMATION FOR SEQ ID NO:442:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human mitochonrial aldehyde dehydrogenase 2 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:442:

TTCCTGACCA TGGTACTTAT AAAAGCAGTG CCGTCTGCCC CATCCATGTC 50

(2) INFORMATION FOR SEQ ID NO:443:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human carbonic anhydrase III gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:443:

AAGGCCATGC AAGTGTGCGG GGGAGCTACA TAAAAGCGCG GGCTCGCGCG 50

(2) INFORMATION FOR SEQ ID NO:444:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human creatine kinase B isozyme gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:444:

TGGGCGGCCC GCGTTGTGCC CCTTAAGAGC CGCGGGAGCG CGGAGCGGCC 50

(2) INFORMATION FOR SEQ ID NO:445:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human preproenkephalin A gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:445:

CTTCGGTTTG GGGCTAATTA TAAAGTGGCT CCAGCAGCCG TTAAGCCCCG 50

(2) INFORMATION FOR SEQ ID NO:446:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human preprokephalin A gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:446:

CTTCGGTTTG GGGCTAATTA TAAAGTGGCT CCAGCAGCCG TTAAGCCCCG G 51

(2) INFORMATION FOR SEQ ID NO:447:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human prepro form of corticotropin releasing factor gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:447:

TTTTTGAAGA GGGTCGACAC TATAAAATCC CACTCCAGGC TCTGGAGTGG 50

(2) INFORMATION FOR SEQ ID NO:448:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human preprothyrotropin-releasing hormone gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:448:

GACCTCACTC GAGCCGCCGC CTGGCGCAGA TATAAGCGGC GGCCCATCTG 50

(2) INFORMATION FOR SEQ ID NO:449:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for fetal A-gamma and G-gamma hemoglobin

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:449:

CGGCTGGCTA GGGATGAAGA ATAAAAGGAA GCACCCTTCA GCAGTTCCAC 50

(2) INFORMATION FOR SEQ ID NO:450:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene coding for ACTH and beta-LPH precursors

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:450:

CCCACCAGGA GAGCTCGGCA AGTATATAAG GACAGAGGAG CGCGGGACCA 50

(2) INFORMATION FOR SEQ ID NO:451:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human somatostatin I gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:451:

TAGCCTGACG TCAGAGAGAG AGTTTAAAAC AGAGGGAGAC GGTTGAGAGC 50

(2) INFORMATION FOR SEQ ID NO:452:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human glucagon gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:452:

GTGAGGCTAA ACAGAGCTGG AGAGTATATA AAAGCAGTGC GCCTTGGTGC 50

(2) INFORMATION FOR SEQ ID NO:453:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human glucagon gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:453:

GTGAGGCTAA ACAGAGCTGG AGAGTATATA AAAGCAGTGC GCCTTGGTGC A 51

(2) INFORMATION FOR SEQ ID NO:454:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human chorionic gonadotropin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:454:

AGGTGGAAAC ACTCTGCTGG TATAAAAGCA GGTGAGGACT TCATTAACTG 50

(2) INFORMATION FOR SEQ ID NO:455:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human chorionic gonadotropin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:455:

TTGAACTGTG GTGCAGGAAA GCCTCAAGTA GAGGAGGGTT GAGGCTTCAA 50

(2) INFORMATION FOR SEQ ID NO:456:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human beta-LH gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:456:

GCCGCCCCCA CAACCCCGAG GTATAAAGCC AGATACACGA GGCAGGGGAT 50

(2) INFORMATION FOR SEQ ID NO:457:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human follicle-stimulating hormone beta-subunit gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:457:

TAGTTGCACA TGATTTTGTA TAAAAGGTGA ACTGAGATTT CATTCAGTCT 50

(2) INFORMATION FOR SEQ ID NO:458:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human prolactin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:458:

TATTCATGAA GATATCAAAG GTTTATAAAG CCAATATCTG GGAAAGAGAA 50

(2) INFORMATION FOR SEQ ID NO:459:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human parathyroid gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:459:

GACATCATCT GTAACAATAA AAGAGCCTCT CTTGGTAAGC AGAAGACCTA 50

(2) INFORMATION FOR SEQ ID NO:460:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Owl monkey insulin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:460:

GGGGAGATGG GCTCTGGGCC TATAAAGCCA GCAGGGACCC AGCAGCCCTC 50

(2) INFORMATION FOR SEQ ID NO:461:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: human insulin/IGF II gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:461:

CCCCGCCTCC AGAGTGGGGG CCAAGGCTGG GCAGGCGGGT GGACGGCCGG 50

(2) INFORMATION FOR SEQ ID NO:462:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human insulin like growth factor IGFII gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:462:

AAAGAACTCT GCCTTGCGTT CCCCAAAATT TGGGCATTGT TCCGGCTCGC 50

(2) INFORMATION FOR SEQ ID NO:463:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human insulin-like growth factor II gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:463:

CCCTGGGCCG CGGCTGGCGC GACTATAAGA GCCGGGCGTG GGCGCCCGCA 50

(2) INFORMATION FOR SEQ ID NO:464:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gastrin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:464:

AGTTGGGAGG GACCTTGAGG GCTTTATAAG GCAGGCCTGG AGCATCAAGC 50

(2) INFORMATION FOR SEQ ID NO:465:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human interferon alpha gene INF-alpha 13

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:465:

GGAAATCAGT ATGTTCCCTA TTTAAGGCAT CTGCAGGAAG CAAAGCCTTC 50

(2) INFORMATION FOR SEQ ID NO:466:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for leukocyte interferon

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:466:

GGAAGCTAGT ATGTTCCTTA TTTAAGACCT ATGCACAGAG CAAGGTCTTC 50

(2) INFORMATION FOR SEQ ID NO:467:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human interferon alpha gene INF-alpha 4b

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:467:

GGAAATTAGT ATGTTCACTA TTTAAGACCT ATGCACAGAG CAAAGTCTTC 50

(2) INFORMATION FOR SEQ ID NO:468:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for leukocyte (alpha) interferon

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:468:

GGAAATTAGT ATGTTCACTA TTTAAGGCCT ATGCACAGAG CAAAGTCTTC 50

(2) INFORMATION FOR SEQ ID NO:469:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human interferon genes LeIF-L and LeIF-J

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:469:

GGAAATTAGT ATGTTCACTA TTTAAGACCT ATGCACAGAG CAAAGTCTTC 50

(2) INFORMATION FOR SEQ ID NO:470:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human gene for fibroblast (beta-1) interferon

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:470:

ATAGAGAGAG GACCATCTCA TATAAATAGG CCATACCCAC GGAGAAAGGA 50

(2) INFORMATION FOR SEQ ID NO:471:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human c-sis gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:471:

CTCTCGCACT CTCCCTTCTC CTTTATAAAG GCCGGAACAG CTGAAAGGGT 50

(2) INFORMATION FOR SEQ ID NO:472:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human migratory inhibitory factor-related protein 8

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:472:

CAGCTGGCCA AGCCTAACCG CTATAAAAAG GAGCTGCCTC TCAGCCCTGC 50

(2) INFORMATION FOR SEQ ID NO:473:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human migratory inhibitory factor-related protein 14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:473:

GTGCCCCAGT CAGGAGCTGC CTATAAATGC CGAGCCTGCA CAGCTCTGGC 50

(2) INFORMATION FOR SEQ ID NO:474:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human epidermal growth factor related gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:474:

GGTCCCTCCT CCTCCCGCCC TGCCTCCCGC GCCTCGGCCC GCGCGAGCTA 50

(2) INFORMATION FOR SEQ ID NO:475:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human opsin gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:475:

GCTTAGGAGG GGGAGGTCAC TTTATAAGGG TCTGGGGGGG TCAGAACCCA 50

(2) INFORMATION FOR SEQ ID NO:476:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human blue cone photoreceptor pigment gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:476:

TTTTGTGGGG TGGGAGGATC ACCTATAAGA GGACTCAGAG GAGGGTGTGG 50

(2) INFORMATION FOR SEQ ID NO:477:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human red cone photoreceptor pigment gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:477:

CGGGCTGATC CCACAGGCCA GTATAAAGCG CCGTGACCCT CAGGTGATGC 50

(2) INFORMATION FOR SEQ ID NO:478:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human green cone photoreceptor pigment gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:478:

CGGGCTGATC CCACTGGCCG GTATAAAGCG CCGTGACCCT CAGGTGACGC 50

(2) INFORMATION FOR SEQ ID NO:479:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human interferon-inducible gene IFI-56K

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:479:

TTGGCTGCTG TTTAGCTCCC TTATATAACA CTGTCTTGGG GTTTAAACGT 50

(2) INFORMATION FOR SEQ ID NO:480:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human interferon-induced 15-Kd protein (ISG) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:480:

GACGTGTGTG CCTCAGGCTT AATAATAGGG CCGGTGCTGC TGCGGAAGCC 50

(2) INFORMATION FOR SEQ ID NO:481:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human ubiquitin-like protein (GdX) gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:481:

TCCAGCGCGC GCGCCCGGGG CGGCGGCGCG CGGCGGGGGG TGGTTGGGGT 50

(2) INFORMATION FOR SEQ ID NO:482:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human exogenous retrovirus erv3 5" long terminal repeat

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:482:

CCGCCCCTGT TGGTTGCATG TATAAAAGTC AAGCCCTGTC ATTGTTCAGG 50

(2) INFORMATION FOR SEQ ID NO:483:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: RNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Bovine leukemia virus

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:483:

ACCTCACCTG CTGATAAATT AATAAAATGC CGGCCCTGTC GAGTTAGCGG 50

(2) INFORMATION FOR SEQ ID NO:484:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: RNA (genomic)

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human T-cell lymphotropic virus type I

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:484:

TCAATAAACT AGCAGGAGTC TATAAAAGCG TGGAGACAGT TCAGGAGGGG 50

(2) INFORMATION FOR SEQ ID NO:485:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: RNA (genomic)

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human T-cell leukemia virus II proviral LTR

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:485:

TCAAAATAAA AGATGCCGAG TCTATAAAAG CGCAAGGACA GTTCAGGAGG 50

(2) INFORMATION FOR SEQ ID NO:486:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: RNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human T-cell Lymphotropic virus type III (HIV-1)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:486:

GGCGAGCCCT CAGATCCTGC ATATAAGCAG CTGCTTTTTG CCTGTACTGG 50

(2) INFORMATION FOR SEQ ID NO:487:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: RNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Aids-associated retrovirus (arv-2;proviral)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:487:

TGGCGTCCCT CAGATGCTGC ATATAAGCAG CTGCTTTTTG CCTGTACTGG 50

(2) INFORMATION FOR SEQ ID NO:488:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: RNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human immunodeficiency virus type 2 (HIV-2)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:488:

GCCCTCATAT TCTCTGTATA AATATACCCG CTAGCTTGCA TTGTACTTCG 50

(2) INFORMATION FOR SEQ ID NO:489:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: RNA (genomic)

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Visna lentivirus, Icelandic strains LV1-1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:489:

CATAACCGCA GATGTAAACA AGTTGCCTAT ATAAGCCGCT TGCTAGCTGG 50

(2) INFORMATION FOR SEQ ID NO:490:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cytomegalovirus strain AD169 gene I

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:490:

GGCGTGTACG GTGGGAGGTC TATATAAGCA GAGCTCGTTT AGTGAACCGT 50

(2) INFORMATION FOR SEQ ID NO:491:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Murine cytomegalovirus intermediate-early gene I

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:491:

GCTGAGCTGC GTTCACGTGG GTATAAGAGG CGCGACCAGC GTCGGTACCG 50

(2) INFORMATION FOR SEQ ID NO:492:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cytomegalovirus intermediate-early glycoprotein UL37

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:492:

CGTCATGTCC GGCATCTTCA TGTATATAAG ACGGTGTTTC AAGACGACGT 50

(2) INFORMATION FOR SEQ ID NO:493:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cytomegalovirus I-E glycoprotein US3 gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:493:

ACAACGTCAC CAAGAAACGC TATATATTCA AAAACACCGT TCAGTCCACA 50

(2) INFORMATION FOR SEQ ID NO:494:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes Simplex Virus type 1 gene I

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:494:

TTTGGGGAGG GGAAAGGCGT GGGGTATAAG TTAGCCCTGG CCCGACAGTC 50

(2) INFORMATION FOR SEQ ID NO:495:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes Simplex Virus type 1 gene II

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:495:

AGCCGGCCCC GGCACCACGG GTATAAGGAC ATCCACCACC CGGCCGGTGG 50

(2) INFORMATION FOR SEQ ID NO:496:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus type II I-E gene II

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:496:

AGCCGGCCCC GGTCGTGCGG GTATAAGGGC AGCCACCGGC CCACTGGGCG 50

(2) INFORMATION FOR SEQ ID NO:497:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus type I I-E gene III

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:497:

TTCCCGCCGG CCCCTGGGAC TATATGAGCC CGAGGACGCC CCGATCGTCC 50

(2) INFORMATION FOR SEQ ID NO:498:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus type II I-E gene III

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:498:

CCCCGCGCGC CCCGAGCGAC TATATCAGCC AGGCGACGGG GCGATCGTCC 50

(2) INFORMATION FOR SEQ ID NO:499:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus type 1 I-E genes IV and V

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:499:

GGGGGCGGGT CTCTCCGGCG CACATAAAGG CCCGGCGCGA CCGACGCCCG 50

(2) INFORMATION FOR SEQ ID NO:500:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus type 2 I-E genes IV and V

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:500:

ACGGGGGGCG GGCCGTTCCT CGCGCACATA AAGGGCCGGC GTCCCGGTCG 50

(2) INFORMATION FOR SEQ ID NO:501:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cytomegalovirus DNA polymersase gene

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:501:

TAGGCGGGCT GGAAAGATGA TGTATAAATA GAGTCTCCGA CGGGGTTCGG 50

(2) INFORMATION FOR SEQ ID NO:502:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cytomegalovirus b' 2.2 kb transcript (start 160513)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:502:

TAGGCGGGCT GGAAAGATGA TGTATAAATA GAGTCTGCGA CGGGGTTCGG 50

(2) INFORMATION FOR SEQ ID NO:503:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cytomegalovirus 2.7 kb transcript (start 4578)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:503:

GCCCGCGCTC GGCAGAGCTA CCATATAAAA ACGCAGGGGT TTAGCAGCTT 50

(2) INFORMATION FOR SEQ ID NO:504:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 b' 82K AlkExo (start 27048)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:504:

CAGCACCAGG AGAGGCTTAA GCTCGGGAGG CAGCGCCACC GACGACAGTA 50

(2) INFORMATION FOR SEQ ID NO:505:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 b' 42K gene (start site 106547)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:505:

ATGGGTTGTG GTTATATGCA CTTCCTATAA GACTCTCCCC CACCGCCCAC 50

(2) INFORMATION FOR SEQ ID NO:506:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 39k dUTPase gene (start 106811)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:506:

CGTGTGCGAT AATACACACG CCCATCGAGG CCATGCCTAC ATAAAAGGGC 50

(2) INFORMATION FOR SEQ ID NO:507:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 b' 33K (start site 145165)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:507:

GGCCGGGCGA CCCAGATGTT TACTTAAAAG GCGTGCCGTC CGCCGGCATG 50

(2) INFORMATION FOR SEQ ID NO:508:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 21K (start site 145459)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:508:

CGACGTACGC GATGAGATCA ATAAAAGGGG GCGTGAGGAC CGGGAGGCGG 50

(2) INFORMATION FOR SEQ ID NO:509:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 b' 5 kb transcript (start 86216)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:509:

CCCCACCCCT GCGCGATGTG GATAAAAAGC CAGCGCGGGT GGTTTAGGGT 50

(2) INFORMATION FOR SEQ ID NO:510:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 b' RNR2 gene (start 89774)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:510:

GGTCCGCCTT CTGGTCCACG CATATAAGCG CGGACTAAAA ACAGGGATGT 50

(2) INFORMATION FOR SEQ ID NO:511:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-2 RNR2 gene (start site 247)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:511:

TGGTCCGCCT TCTCGTCCAC GCATATAAGC GCGGCCTGAA GACGGGGATG 50

(2) INFORMATION FOR SEQ ID NO:512:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 b' tk gene (start site 47911)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:512:

CGCGGTCCCA GGTCCACTTC GCATATTAAG GTGACGCGTG TGGCCTCGAA 50

(2) INFORMATION FOR SEQ ID NO:513:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-2 b' tk gene (start site 225)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:513:

CGCGGCCCGA GGTCCACTTC GCATATTAAG GTGACGCGCG TGGCCTCGAA 50

(2) INFORMATION FOR SEQ ID NO:514:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 b' dbp gene (start site 62318)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:514:

CGGCACGCCC CCAGGTAAAG TGTACATATA CCAACCGCAT ACCAGACGCA 50

(2) INFORMATION FOR SEQ ID NO:515:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 b' gB (3.3 Kb) start 56081

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:515:

CCACTCAGCG CGCCGCCTGG CGATATATTC GCGAGCTGAT TATCGCCACC 50

(2) INFORMATION FOR SEQ ID NO:516:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 b' gD (start 138337)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:516:

CCACTCAGCG CGCCGCCTGG CGATATATTC GCGAGCTGAT TATCGCCACC 50

(2) INFORMATION FOR SEQ ID NO:517:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-2 b' gD (start 5918)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:517:

GGAGTATAAT AGAGTCTTTG TGTTTAAAAC CCGGGCTCGG TGTGGTGTTC 50

(2) INFORMATION FOR SEQ ID NO:518:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 b' gE (start site 141171)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:518:

GGAGAGGGCC CGCGGCGCAT TTAAGGCGTT GTTGTGTTGA CTTTGCCTCT 50

(2) INFORMATION FOR SEQ ID NO:519:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 ICP gene (start site 58361)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:519:

AATTATTGCT ACGACATCCG TGCTTGTTTG TGTTCCGTGT CTATATCTCT 50

(2) INFORMATION FOR SEQ ID NO:520:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 b' tr-4 (start site 136729)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:520:

GGCGGTGCTG TTTGCGGGTT GGCACAAAAA GACCCCGATC CGCGTCTGTG 50

(2) INFORMATION FOR SEQ ID NO:521:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 [U-S] b' tr-9 (start 143245)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:521:

GTGACGTCAA TTGCCCGAGC CGCATAAAGG GCCGGTGGTC CGCCTAGCCG 50

(2) INFORMATION FOR SEQ ID NO:522:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 b'g' VP5 (start 40768)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:522:

GGGGTGGGGC GGGGGGGGGG GTATATAAGG CCTGGGATCC CACGTCCCCG 50

(2) INFORMATION FOR SEQ ID NO:523:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 b'g' 2.1kb transcript (start 26639)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:523:

CCCGTTAACC CCCCACGTGA TCAGCACGCC ACCGACACCG CAGACGAAAA 50

(2) INFORMATION FOR SEQ ID NO:524:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 b'g' a'TIF/VSP (start 105259)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:524:

GGGGCGGCCC GTGCGGGTTG CTTAAATGCG TGGTGGCGAC CACGGGCTGT 50

(2) INFORMATION FOR SEQ ID NO:525:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 b'g' 2.7 kb transcript (start 100998)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:525:

GCCACGCCCA TAAGCTCCTC CCGATAAAAA CCGCCCCGAT GGCCCTGGAC 50

(2) INFORMATION FOR SEQ ID NO:526:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cytomegalovirus UL36 gene (start 49862)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:526:

GACGTCAACG CTGATAGTGT CTATAAAGGC CGTGCCGCCG CGCCGTAGTT 50

(2) INFORMATION FOR SEQ ID NO:527:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cytomegalovirus g' pp65 gene (start 121072)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:527:

TCCGCGTTTG GTCGCCTGCC TATGTAAGGC GGCGGCCGCA GAGGGCGCGC 50

(2) INFORMATION FOR SEQ ID NO:528:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cytomegalovirus g' pp71 gene (start 119223)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:528:

GTCACCGCTG CTATATTTGC GACAGTTGCC GGAACCCTTC CCGACCTCCC 50

(2) INFORMATION FOR SEQ ID NO:529:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human cytomegalovirus g' pp150 gene (start 43092)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:529:

CGTATCCGCC TCCGCTATTA AACTACCCCC CCTCCCTCTA GGTGGGGCGC 50

(2) INFORMATION FOR SEQ ID NO:530:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 g' 5 Kb transcript (start 103313)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:530:

TTGTGTCGCA GGGCGGCCCG CGTATAAAGG CGAGAGCGCG GGACCGTTTC 50

(2) INFORMATION FOR SEQ ID NO:531:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 g' gC (start 96170)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:531:

AACCCCGGAT GGGGCCCGGG TATAAATTCC GGAAGGGGAC ACGGGCTACC 50

(2) INFORMATION FOR SEQ ID NO:532:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-2 g' gC (start 670)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:532:

GCGGGGGTGC CGTGGACGGG TATAAAGGCC AGGGGGGCAC GCGGGCCCAT 50

(2) INFORMATION FOR SEQ ID NO:533:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 g' gH gene (start 46581)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:533:

CGGCAATAAA AAGACAGAAT AAAACGCACG GGTGTTGGGT CGTTTGTTCA 50

(2) INFORMATION FOR SEQ ID NO:534:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 g' 42 K (start site 107130)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:534:

CCGGAGTCCC CGCTAACCTT CGGCATAAAA GCCACCGCGC GCCTGTTGAC 50

(2) INFORMATION FOR SEQ ID NO:535:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 Ori_s ORF (start site 132287)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:535:

CGGAGGCCCC CGGGGTGCGT CCCCTGTGTT TCGTGGGTGG GGTGGGCGGG 50

(2) INFORMATION FOR SEQ ID NO:536:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-1 18 K (start site 97951)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:536:

CCCGCCCACC GCTGGGCGCT ATAAAGCCGC CACCCTCTCT TCCCTCAGGT 50

(2) INFORMATION FOR SEQ ID NO:537:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Herpes simplex virus-2 18K (start site 2391)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:537:

CCCCGCCGTC CCCCGGGCGT TATAAGCCGC CGCACTCGCT TTTCCCACCG 50

(2) INFORMATION FOR SEQ ID NO:538:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Epstein Barr virus L1 1Kb gene (start site 103194)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:538:

TGGTGCCTTG GCTTTAAAGG GGAGATGTTA GACAGGTAAC TCACTAAACA 50

(2) INFORMATION FOR SEQ ID NO:539:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Epstein Barr virus R1 145K gene (start site 1721)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:539:

ACTGTATAAA GGTAAGTATT ATTAAATTTT AGAGACACTA TCACGTGTAA 50

(2) INFORMATION FOR SEQ ID NO:540:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Epstein Barr virus R1 20K (start site 9660)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:540:

CTTTTAGCCA TGCCATGCTC TATAAATCAC TTCCCTATCT CAGGTAGGCC 50

(2) INFORMATION FOR SEQ ID NO:541:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Epstein Barr virus [DL/R] (start site 52787)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:541:

ACAGAGACCC CAAAAAGAGG ATAAAAGAAG GCGAGCCGGC CCGGCTCGCC 50

(2) INFORMATION FOR SEQ ID NO:542:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Epstein Barr virus R2 (start site 61372)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:542:

GTGACGGTCA GGCAGCTCCT GTATTTAACT TTGCGGACAG AGGCCAGAGC 50

(2) INFORMATION FOR SEQ ID NO:543:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Epstein Barr virus L2 (start site 57050)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:543:

TAATTACGCT TGTGTACATA TTTAAATCCA CACAAGTGGC CAGAGTGGGC 50

(2) INFORMATION FOR SEQ ID NO:544:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Epstein Barr virus R1 (start site 88539)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:544:

GACAGGGACG GCGGCGCTAT ATATAAGAGC CCAAGACCCG GCTCTCTTTA 50

(2) INFORMATION FOR SEQ ID NO:545:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Epstein Barr virus R2 (start site 88897)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:545:

CGGATTAGAT GGGGATATTT AAAAGGGGCA GCAATCTCGG CTGTTTGTAC 50

(2) INFORMATION FOR SEQ ID NO:546:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Epstein Barr virus L2 (start site 90021)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:546:

ACCCAACAGG TGGTGAAAAT ATAACACAGG TGACACCAGC CTCTATCAGC 50

(2) INFORMATION FOR SEQ ID NO:547:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Epstein Barr virus [BamH1-L] L1
(start site 92157)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:547:

ACCCCCCTTG TACCTATTAA AGAGGATGCT GCCTAGAAAT CGGTGCCGAG 50

(2) INFORMATION FOR SEQ ID NO:548:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Epstein Barr virus [BamH1-L] L3
(start site 88480)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:548:

CGGGTCTTGG GCTCTTATAT ATAGCGCCGC CGTCCCTGTC TGTTAGATCA 50

(2) INFORMATION FOR SEQ ID NO:549:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Epstein Barr virus [BamH1-K] 2.1 Kb (start site 109939)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:549:

AGACGCCCTC AATCGTATTA AAAGCCGTGT ATTCCCCCGC ACTAAAGAAT 50

(2) INFORMATION FOR SEQ ID NO:550:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Epstein Barr virus [BamH1-K] 1.3kb transcript (start 110632)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:550:

TTGCGACCCC TCTGATATTA AGGTGGTTAT TTTGGGCCAG GACCCCTATC 50

(2) INFORMATION FOR SEQ ID NO:551:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Epstein Barr virus [EcoR1-H] L1 (start site 137680)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:551:

CGGTGCCCGG ACTCAGAATT ATTAAACCGG GTGGCAGCTC CTGGCAGTCA 50

(2) INFORMATION FOR SEQ ID NO:552:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Epstein Barr virus [EcoR1-D] L1 (start site 159337)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:552:

AAGGGCAGGG GGTGGGTATT TAAGGATCTA TATGCCCTTC TCTACCTGCA 50

(2) INFORMATION FOR SEQ ID NO:553:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Epstein Barr virus [EcoR1-D] R1 (start 165496)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:553:

AATGGGCGTG GCAGAATAGT ATAAGACGCG AGGCCTGGGT GAGGAGAGTC 50

(2) INFORMATION FOR SEQ ID NO:554:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Epstein Barr virus [EcoR1-D] L2 (start 167495)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:554:

TCTTTCCTTG TCCTTACTGT ATAAAAGTCC ACGAAAACAG CTGTGCCTCA 50

(2) INFORMATION FOR SEQ ID NO:555:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Epstein Barr Virus [EcoR1-D] L1A start 169165

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:555:

ACTGATGAGT AAGTATTACA CCCTTTGCCC CACACCCCCT TTCCCTTACT 50

(2) INFORMATION FOR SEQ ID NO:556:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Epstein Barr Virus [EBNA] E1 (start site 11333)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:556:

AGGGGGGGAC TAAGGTCCCA CTACAAAAAC TCTGTGTTCT GCTGCAAATT 50

(2) INFORMATION FOR SEQ ID NO:557:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Epstein Barr virus [EBNA] E2 (start site 14399)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:557:

GGTATAAAGT GGTCCTGCAG CTATTTCTGG TCGCATCAGA GCGCCAGGAG 50

(2) INFORMATION FOR SEQ ID NO:558:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Epstein Barr virus [EcoR1-D] L1 (start site 169514)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:558:

CTCTGACGTA GCCGCCCTAC ATAAGCCTCT CACACTGCTC TGCCCCCTTC 50

(2) INFORMATION FOR SEQ ID NO:559:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type 2 EIa (start 498)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:559:

GTCAGCTGAC GCGCAGTGTA TTTATACCCG GTGAGTTCCT CAAGAGGCCA 50

(2) INFORMATION FOR SEQ ID NO:560:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type-5 EIa (start 499)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:560:

GTCAGCTGAC GTGTAGTGTA TTTATACCCG GTGAGTTCCT CAAGAGGCCA 50

(2) INFORMATION FOR SEQ ID NO:561:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type-7 EIa (start site 512)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:561:

TCAGCTGATC GCTAGGGTAT TTAAACCTGA CGAGTTCCGT CAAGAGGCCA 50

(2) INFORMATION FOR SEQ ID NO:562:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type-12 Ela (start site 306)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:562:

AAATTGATGA CGGCAATTTT ATTATAGGCG CGGAATATTT ACCGAGGGCA 50

(2) INFORMATION FOR SEQ ID NO:563:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type-12 EIa (start site 445)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:563:

GTCAGCTGAT CGTTTGGGTA TTTAATGCCG CCGTGTTCGT CAAGAGGCCA 50

(2) INFORMATION FOR SEQ ID NO:564:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Simian Adenovirus SA7 EIa (start site 440)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:564:

TTATTGTCTA GGTGAGGGTA TTTAAACCGG CTCAGACCGT CAAGAGGCCA 50

(2) INFORMATION FOR SEQ ID NO:565:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type-2 EIb (start 1700)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:565:

GGGGCGGCGC TTAAAGGGTA TATAATGCGC CGTGGGCTAA TCTTGGTTAC 50

(2) INFORMATION FOR SEQ ID NO:566:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type-5 EIb (start site 1703)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:566:

GGGGCGGGGC TTAAAGGGTA TATAATGCGC CGTGGGCTAA TCTTGGTTAC 50

(2) INFORMATION FOR SEQ ID NO:567:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type-7 EIb (start site 1577)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:567:

TTCTTGGGTG GGGTCTTGGA TATATAAGTA GGAGCAGATC TGTGTGGTTA 50

(2) INFORMATION FOR SEQ ID NO:568:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type-12 EIb (start site 1527)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:568:

TGGGCGTGGT TAAACAGGGA TATAAAGCTG GGTTGGTGTT GCTTTGAATA 50

(2) INFORMATION FOR SEQ ID NO:569:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type-2 EII (start site 27092)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:569:

GAAAGGGCGC GAAACTAGTC CTTAAGAGTC AGCGCGCAGT ATTTGCTGAA 50

(2) INFORMATION FOR SEQ ID NO:570:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type-2 EIII (start site 27610)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:570:

TGCGGTCGCC CGGGCAGGGT ATAACTCACC TGAAAATCAG AGGGCGAGGT 50

(2) INFORMATION FOR SEQ ID NO:571:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type-5 EIII (start site 239)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:571:

TGCGGTCGCC CGGGCAGGGT ATAACTCACC TGACTCTTGG AGGGCGAGGT 50

(2) INFORMATION FOR SEQ ID NO:572:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type-2 EIV (start site 35611)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:572:

TTACGTCATT TTTTAGTCCT ATATATACTC GCTCTGTACT TGGCCCTTTT 50

(2) INFORMATION FOR SEQ ID NO:573:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type-2 IVa2 (start site 5827)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:573:

CCCTCCCACT TAGCCTCCTT CGTGCTGGCC TGGACGCGAG CCTTCGTCTC 50

(2) INFORMATION FOR SEQ ID NO:574:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type-5 IVa2 (start site 5837)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:574:

CCCTCCCACT TAGCCTCCTT CGTGCTGGCC TGGACGCGAG CCTTTGTCTC 50

(2) INFORMATION FOR SEQ ID NO:575:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type-7 IVa2 (start site 5692)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:575:

CCCTCCCACG TGGCCTCCTT TGTGCTGGCC TGGACACGCG CTTTTGTATC 50

(2) INFORMATION FOR SEQ ID NO:576:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type-2 IX (start site 3575)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:576:

GCTTAAGGGT GGGAAAGAAT ATATAAGGTG GGGGTCTCAT GTAGTTTTGT 50

(2) INFORMATION FOR SEQ ID NO:577:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type-5 IX (start site 3581)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:577:

GCTTAAGGGT GGGAAAGAAT ATATAAGGTG GGGGTCTTAT GTAGTTTTGT 50

(2) INFORMATION FOR SEQ ID NO:578:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type-7 IX (start site 3460)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:578:

ATGGGGACTT TCAGGTTGGT AAGGTGGACA AATTGGGTAA ATTTTGTTAA 50

(2) INFORMATION FOR SEQ ID NO:579:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type-2 major late (start site 6039)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:579:

GTGTTCCTGA AGGGGGGCTA TAAAAGGGGG TGGGGGCGCG TTCGTCCTCA 50

(2) INFORMATION FOR SEQ ID NO:580:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type-5 major late (start site 6049)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:580:

GTGTTCCTGA AGGGGGGCTA TAAAAGGGGG TGGGGGCGCG TTCGTCCTCA 50

(2) INFORMATION FOR SEQ ID NO:581:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type-7 major late (start site 5904)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:581:

GGGTCCCCGC CGGGGGGGTA TAAAAGGGGG CGGACCTCTG TTCGTCCTCA 50

(2) INFORMATION FOR SEQ ID NO:582:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type-12 major late (start site 972)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:582:

AATTTTCTGG TGGTGGGCTA TAAAAAGGGG CGGGTCCTTG GTCTTCATCG 50

(2) INFORMATION FOR SEQ ID NO:583:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Adenovirus type-2 LIIa (start site 25954)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:583:

GGCGTGGTAG TCCTCAGGTA CAAATTTGCG AAGGTAAGCC GACGTCCACA 50

(2) INFORMATION FOR SEQ ID NO:584:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human papilloma virus type 18 E6 gene (start site 30)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:584:

CAGCACATAC TATACTTTTC ATTAATACTT TTAACAATTG TAGTATATAA 50

(2) INFORMATION FOR SEQ ID NO:585:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human papilloma virus type-16 E6/E7 (start site 97)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:585:

GAACCGAAAC CGGTTAGTAT AAAAGCAGAC ATTTTATGCA CCAAAAGAGA 50

(2) INFORMATION FOR SEQ ID NO:586:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human papilloma virus type-18 E6 (start site 105)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:586:

GGACCGAAAA CGGTGTATAT AAAAGATGTG AGAAACACAC CACAATACTA 50

(2) INFORMATION FOR SEQ ID NO:587:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Parvovirus h-1 H-1[+.04] (start site 209)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:587:

AGTGGGCGTG GCTAACTGTA TATAAGCAGT CACTCTGGTC GGTTACTCAC 50

(2) INFORMATION FOR SEQ ID NO:588:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Parvovirus h-1 H-1 [+.40] (start site 2010)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:588:

GCCGAAGCTA GACACTCCTA TAAATTCGCT AGGTTCAATG CGCTCACCAT 50

(2) INFORMATION FOR SEQ ID NO:589:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Human parvovirus B19-Au B19 [0.06] (start site 347)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:589:

GAGCGTAGGC GGGGACTACA GTATATATAG CACGGTACTG CCGCAGCTCT 50

(2) INFORMATION FOR SEQ ID NO:590:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Simian virus 40 T/t late (start site 31)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:590:

CCGCCCCTAA CTCCGCCCAG TTCCGCCCAT TCTCCGCCCC ATGGCTGACT 50

(2) INFORMATION FOR SEQ ID NO:591:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Simian virus 40 T/t early P2 (start site 5233)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:591:

TGGCTGACTA ATTTTTTTTA TTTATGCAGA GGCCGAGGCC GCCTCGGCCT 50

(2) INFORMATION FOR SEQ ID NO:592:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: BK virus T/t early (start site 99)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:592:

CCTGTGGCCT TTTTTTTTAT AATATATAAG AGGCCGAGGC CGCCTCTGCC 50

(2) INFORMATION FOR SEQ ID NO:593:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Polyoma virus T/t E (start site 156)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:593:

GGCCACCCAA ATTGATATAA TTAAGCCCCA ACCGCCTCTT CCCGCCTCAT 50

(2) INFORMATION FOR SEQ ID NO:594:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Simian virus 40 late (start site 325)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:594:

GTTCTTTCCG CCTCAGAAGG TACCTAACCA AGTTCCTCTT TCAGAGGTTA 50

(2) INFORMATION FOR SEQ ID NO:595:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Hepatitis B virus subtype adr4 3.6kb P1 (start 1659)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:595:

AGTTGGGGGA GGAGATTAGG TTAAAGGTCT TTGTACTAGG AGGCTGTAGG 50

(2) INFORMATION FOR SEQ ID NO:596:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Heptitis B virus subtype adr4 3.6 kb P2 (start 1690)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:596:

TGTACTAGGA GGCTGTAGGC ATAAATTGGT CTGTTCACCA GCACCATGCA 50

(2) INFORMATION FOR SEQ ID NO:597:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Hepatitis B virus subtype adr4 2.2 kb P1 (start 3061)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:597:

ATCGGCACTC AGGAAGACAG CCTACTCCCA TCTCTCCACC TCTAAGAGAC 50

(2) INFORMATION FOR SEQ ID NO:598:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Hepatitis B virus subtype adr4 2.2 kb P2 (start 3092)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:598:

CTCTCCACCT CTAAGAGACA GTCATCCTCA GGCCATGCAG TGGAACTCCA 50

(2) INFORMATION FOR SEQ ID NO:599:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Epstein Barr virus [BamH1-F] R1 (start 58862)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:599:

TATTTTTGAA AAGGGATATT ATAAAACAGG TCATTGCTCG GATTGTGGCA 50

(2) INFORMATION FOR SEQ ID NO:600:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 56 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Promoter Sequenc of IL-13

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:600:

GGTGTGAGGC GTCACCACTT GGGCCTATAA AAGCTGCCAC AAGACGCCAA GGCCAC 56

(2) INFORMATION FOR SEQ ID NO:601:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: UL9 BINDING SITE, HSV oriS, higher affinity

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:601:

CGTTCGCACT T 11

(2) INFORMATION FOR SEQ ID NO:602:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: UL9 BINDING SITE, HSV oriS, lower affinity

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:602:

TGCTCGCACT T 11

(2) INFORMATION FOR SEQ ID NO:603:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: UL9Z1 TEST SEQ. / UL9 ASSAY SEQ.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:603:

GCGCGCGCGC GTTCGCACTT CCGCCGCCGG 30

(2) INFORMATION FOR SEQ ID NO:604:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: UL9Z2 TEST SEQ. / UL9 ASSAY SEQ.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:604:

GGCGCCGGCC GTTCGCACTT CGCGCGCGCG 30

(2) INFORMATION FOR SEQ ID NO:605:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: UL9 CCCG TEST SEQ. / UL9 ASSAY SEQ.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:605:

GGCCCGCCCC GTTCGCACTT CCCGCCCCGG 30

(2) INFORMATION FOR SEQ ID NO:606:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: UL9 GGGC TEST SEQ. / UL9 ASSAY SEQ.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:606:

GGCGGGCGCC GTTCGCACTT GGGCGGGCGG 30

(2) INFORMATION FOR SEQ ID NO:607:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: UL9 ATAT TEST SEQ. / UL9 ASSAY SEQ.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:607:

GGATATATAC GTTCGCACTT TAATTATTGG 30

(2) INFORMATION FOR SEQ ID NO:608:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: UL9 polyA TEST SEQ. / UL9 ASSAY SEQ.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:608:

GGAAAAAAAC GTTCGCACTT AAAAAAAAGG 30

(2) INFORMATION FOR SEQ ID NO:609:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: UL9 polyT TEST SEQ. / UL9 ASSAY SEQ.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:609:

GGTTTTTTTC GTTCGCACTT TTTTTTTTGG 30

(2) INFORMATION FOR SEQ ID NO:610:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: UL9 GCAC TEST SEQ. / UL9 ASSAY SEQ.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:610:

GGACGCACGC GTTCGCACTT GCAGCAGCGG 30

(2) INFORMATION FOR SEQ ID NO:611:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: UL9 ATori-1 Test sequence / UL9 ASSAY SEQ.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:611:

GCGTATATAT CGTTCGCACT TCGTCCCAAT 30

(2) INFORMATION FOR SEQ ID NO:612:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: oriECO2 TEST SEQ. / UL9 ASSAY SEQ.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:612:

GGCGAATTCG ACGTTCGCAC TTCGTCCCAA T 31

(2) INFORMATION FOR SEQ ID NO:613:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: oriECO3 TEST SEQ. / UL9 ASSAY SEQ.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:613:

GGCGAATTCG ATCGTTCGCA CTTCGTCCCA AT 32

(2) INFORMATION FOR SEQ ID NO:614:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE· NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: WILD TYPE

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:614:

AAGTGAGAAT TCGAAGCGTT CGCACTTCGT CCCAAT 36

(2) INFORMATION FOR SEQ ID NO:615:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: TRUNCATED UL9 BINDING SITE, COMPARE SEQ ID NO:601

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:615:

TTCGCACTT 9

(2) INFORMATION FOR SEQ ID NO:616:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: HSVB1/4, SEQUENCE OF COMPETITOR DNA MOLECULE

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:616:

GGTCGTTCGC ACTTCGC 17

(2) INFORMATION FOR SEQ ID NO:617:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Figure 14B, top strand of an exemplary target sequence

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:617:

GCGTANNNNN CGTTCGCACT TNNNNCTTCG TCCCAAT 37

(2) INFORMATION FOR SEQ ID NO:618:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: HSV primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:618:

ATTGGGACGA AG 12

(2) INFORMATION FOR SEQ ID NO:619:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: a sample distamycin target sequence

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:619:

TTCCTCCTTT C 11

(2) INFORMATION FOR SEQ ID NO:620:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: a distamycin target sequence

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:620:

TTCCNNNTTT C 11

(2) INFORMATION FOR SEQ ID NO:621:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: YES

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Figure 27A, test oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:621:

GCGTANNNNN CGTTCGCACT TNNNNCTTCG TCCCAAT 37

(2) INFORMATION FOR SEQ ID NO:622:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: YES

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Figure 27B, oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:622:

GCGTANNNNN CGTTCGCACT TNNNNCTTCG TCCCAAT 37

(2) INFORMATION FOR SEQ ID NO:623:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 37 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: YES

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Figure 27C, oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:623:

GCGTANNNNN TTCACGCTTG CNNNNCTTCG TCCCAAT 37

(2) INFORMATION FOR SEQ ID NO:624:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: YES

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Figure 27D, oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:624:

GCGTANNNNN TTCACGCTTG CNNNNCTTCG TCCCAAT 37

(2) INFORMATION FOR SEQ ID NO:625:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: -35 region consensus sequence

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:625:

TTGACA 6

(2) INFORMATION FOR SEQ ID NO:626:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: -10 region consensus sequence

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:626:

TATAAT 6

(2) INFORMATION FOR SEQ ID NO:627:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 242 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: HIV-1, LTR sequence, Figure 28

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:627:

GTTAGAGTGG AGGTTTGACA GCCGCCTAGC ATTTCATCAC ATGGCCCGAG AGCTGCATCC 60

GGAGTACTTC AAGAACTGCT GACATCGAGC TTGCTACAAG GGACTTTCCG CTGGGGACTT 120

TCCAGGGAGG CGTGGCCTGG GCGGGACTGG GGAGTGGCGA GCCCTCAGAT CCTGCATATA 180

AGCAGCTGCT TTTTGCCTGT ACTGGGTCTC TCTGGTTAGA CCAGATCTGA GCCTGGGAGC 240

TC 242

(2) INFORMATION FOR SEQ ID NO:628:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: a TFIID binding site

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:628:

CCTGCATA 8

(2) INFORMATION FOR SEQ ID NO:629:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: a TFIID binding site

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:629:

AAGCAGCT 8

(2) INFORMATION FOR SEQ ID NO:630:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Oligonucleotide, Figure 29A

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:630:

GCAGAATTCT GCAG 14

(2) INFORMATION FOR SEQ ID NO:631:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Oligonucleotide, Figure 29A

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:631:

GCAGAATTCT GCAGCGTTCG CACTTTCTAG AGCTCAGG 38

(2) INFORMATION FOR SEQ ID NO:632:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Oligonucleotide, Figure 29A

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:632:

AGATCTCGAG TCC 13

(2) INFORMATION FOR SEQ ID NO:633:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Oligonucleotide, Figure 29B

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:633:

GCAGAATTCT GCAGNNNNCG TTCGCACTTT CTAGAGCTCA GG 42

(2) INFORMATION FOR SEQ ID NO:634:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Oligonucleotide, Figure 29C

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:634:

GCAGAATTCT GCAGNNNNNN NNCGTTCGCA CTTTCTAGAG CTCAGG 46

(2) INFORMATION FOR SEQ ID NO:635:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Oligonucleotide, Figure 29D

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:635:

GCAGAATTCT GCAGCGTTCG CACTTNNNNN NNNTCTAGAG CTCAGG 46

(2) INFORMATION FOR SEQ ID NO:636:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Oligonucleotide, Figure 30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:636:

CGTGAATTCT GCAG 14

(2) INFORMATION FOR SEQ ID NO:637:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Oligonucleotide, Figure 30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:637:

CGTGAATTCT GCAGATG 17

(2) INFORMATION FOR SEQ ID NO:638:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 54 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Oligonucleotide, Figure 30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:638:

CGTGAATTCT GCAGATGAGG TACCNNNNNN CGTTCGCACT TTCTAGAGCT CTCC 54

(2) INFORMATION FOR SEQ ID NO:639:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Oligonucleotide, Figure 30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:639:

GTGAAAGATC TCGAGAGG 18

(2) INFORMATION FOR SEQ ID NO:640:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: Oligonucleotide, Figure 30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:640:

AAGATCTCGA GAGG 14

(2) INFORMATION FOR SEQ ID NO:641:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: UL9 BINDING SITE, HSV oriS

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:641:

CGTTCTCACT T 11

IT IS CLAIMED:

1. A method of constructing a DNA-binding agent capable of sequence-specific binding to a duplex DNA target region, comprising:

identifying in the duplex DNA, a target region containing a series of at least two non-overlapping base-pair sequences of four base-pairs each, where the four base-pair sequences are adjacent and each sequence is characterized by sequence-preferential binding to a small molecule, and

coupling the small molecules to form a DNA-binding agent capable of sequence-specific binding to said target region.

2. The method of claim 1, where the duplex binding small molecules are identified as molecules capable of binding to a selected test sequence in a duplex DNA by:

(i) adding a molecule to be screened to a test system composed of (a) a duplex DNA test oligonucleotide having a screening sequence adjacent a selected test sequence, where a DNA binding protein is effective to bind to said screening sequence with a binding affinity that is substantially independent of such test sequence, but where DNA protein binding to the screening sequence is sensitive to binding of test molecules to such test sequence, and (b) said DNA-binding protein,

(ii) incubating the molecule in the test system for a period sufficient to permit binding of the molecule being tested to the test sequence in the duplex DNA, and

(iii) comparing the amount of binding protein bound to the duplex DNA test oligonucleotide before and after said adding.

3. The method of claim 2, where the screening sequence is from the HSV origin of replication and the binding protein is UL9.

4. The method of claim 3, wherein the DNA screening sequence is selected from the group consisting of SEQ ID NO:601, SEQ ID NO:602, SEQ ID NO:615, and SEQ ID NO:641.

5. The method of claim 2, where said comparing is accomplished using either a gel band-shift assay or a filter-binding assay.

6. The method of claim 1, where the subunits are the same and the DNA-binding agent is a homopolymer.

7. The method of claim 1, where the subunits are different and the DNA-binding agent is a heteropolymer.

8. The method of claim 1, where the four base pair sequences are separated by at least 1-6 basepairs.

9. The method of claim 1, where said DNA-binding small molecules are coupled to each other using a spacer molecule.

10. The method of claim 1, where the two sequences are selected from the group of sequences consisting of TTTC, TTTG, TTAC, TTAG, TTGC, TTGG, TTCC, TTCG,

TATC, TATG, TAAC, TAAG, TAGC, TAGG, TACC, TAGC sequences.

11. The method of claim 10, where the duplex DNA-binding small molecule is distamycin.

12. A method of blocking transcription activity from a duplex DNA template, comprising

identifying in the duplex DNA a binding site for a transcription factor and, adjacent the binding site, a target region having series of at least two non-overlapping base-pair sequences of four base-pairs each, where the four base-pair sequences are adjacent and each sequence is characterized by sequence-preferential binding to a small molecule, and

contacting the duplex DNA with a binding agent composed of the small molecules coupled to form a DNA-binding agent capable of sequence-specific binding to said target region.

13. The method of claim 12, where the target region is selected from DNA sequences adjacent a binding site for a eucaryotic transcription factor.

14. The method of claim 13, where the transcription factor is TFIID.

15. The method of claim 12, where the target region is selected from DNA sequences adjacent a binding site for a procaryotic transcription factor.

16. The method of claim 15, where the transcription factor is a sigma factor.

17. A DNA-binding agent capable of binding with base-sequence specificity to a target region in duplex DNA, where the target region contains at least two adjacent four base-pair sequences, comprising

at least two subunits, where each subunit is a small molecule and has a sequence-preferential binding affinity for a sequence of four base-pairs in the target region, and

where the subunits are coupled to form a DNA-binding agent capable of sequence-specific binding to said target region.

18. A method of constructing a binding agent capable of sequence-specific binding to a duplex DNA target region, comprising:

identifying in the duplex DNA, a target region containing (i) a series of at least two adjacent non-overlapping base-pair sequences of four base-pairs each, where each four base-pair sequence is characterized by sequence-preferential biding to a small molecule, and (ii) adjacent to (i) a DNA duplex region capable of forming a triplex with a third-strand oligonucleotide,

coupling the small molecules to form a DNA-binding agent capable of sequence-specific binding to said target region, and

attaching the DNA-binding agent to a third strand oligonucleotide.

19. The method of claim 18, where binding of the DNA-binding agent to duplex DNA causes a shift from B form to A form DNA.

20. A DNA-binding agent capable of binding with base-s quence sp cificity to a duplex DNA target region

containing two sites, a first site having at least two adjacent four base pair sequences, and a second site capable of forming a triplex with a third-strand oligonucleotide, said DNA-binding agent comprising

at least two subunits, where each subunit is a small molecule and has a sequence-preferential binding affinity for a sequence of four base-pairs in the target region, where the subunits are coupled to form a DNA-binding agent capable of sequence-specific binding to said first site, and

a third strand capable of forming a triplex with the second site,

where the third strand is attached to the DNA-binding agent.

21. A method of ordering the sequence binding preferences of a DNA-binding molecule, comprising

(i) adding a molecule to be screened to a test system composed of (a) a duplex DNA test oligonucleotide having a screening sequence adjacent a selected test sequence, where a DNA binding protein is effective to bind to said screening sequence with a binding affinity that is substantially independent of such test sequence, but where DNA protein binding to the screening sequence is sensitive to binding of test molecules to such test sequence, and (b) said DNA-binding protein,

(ii) incubating the molecule in the test system for a period sufficient to permit binding of the molecule being tested to the test sequence in the duplex DNA,

(iii) comparing the amount of binding protein bound to the duplex DNA test oligonucleotide before and after said adding,

(iv) repeating steps (i) and (iii) using duplex DNA test oligonucleotides containing all test sequences of interest, and

(v) ordering the relative amounts of protein to each duplex DNA test oligonucleotide bound in the presence of the molecule for each test sequence.

22. The method of claim 21, where the test sequences are selected from the group of 256 possible four base sequences composed of A, G, C and T.

23. A method for altering the binding characteristics of a DNA-binding protein to a duplex DNA, comprising

identifying in the duplex DNA (i) a binding site for the DNA-binding protein, where said site comprises a series of contiguous paired nucleotides, and (ii) a target region adjacent the binding site,

selecting a small molecule characterized by sequence-preferential binding to the target region, where, when the small molecule is bound to the target region, the small molecule is adjacent to the site for the DNA-binding protein or overlapping the site for the DNA-binding protein by at least one nucleotide pair, and

contacting the duplex DNA with the small molecule at a concentration effective to alter binding of the DNA-binding protein to its binding site.

24. The method of claim 23, where contacting the duplex DNA with the small molecule inhibits the binding of the DNA-binding protein to its binding site.

25. The method of claim 23, where contacting the duplex DNA with the small molecule enhances the binding of the DNA-binding protein to its binding site.

26. The method of claim 23, where the DNA binding protein is a eucaryotic general transcription factor and the target region is selected from DNA sequences adjacent the binding site for the eucaryotic transcription factor.

27. The method of claim 26, where the transcription factor is TFIID.

28. The method of claim 27, where the region is selected from the group of DNA sequences consisting of SEQ ID NO:1 to SEQ ID NO:600.

29. The method of claim 23, where the DNA binding protein is a eucaryotic general transcription factor and the small molecule binds, in addition to the target region, 1 to three nucleotide pairs of the DNA-binding protein's binding site.

30. The method of claim 29, where the eucaryotic general transcription factor is TFIID, and the small molecule binds to (i) the target region, and (ii) up to two nucleotides of the binding site for the eucaryotic transcription factor, where the nucleotides are contiguous to the target region.

31. The method of claim 23, where the DNA binding protein is a DNA replication factor.

32. A method of identifying test sequences in duplex DNA to which binding of a test molecule is most preferred, comprising

(i) constructing a mixture of duplex DNA test oligonucleotides, where each oligonucleotide has (a) a screening sequence adjacent (b) a test sequence, where a DNA binding protein is effective to bind to said screening sequence with a binding affinity that is substantially independent of such test sequence, but where DNA protein binding to the screening sequence is sensitive to binding of test molecules to such test sequence, and (c) where test oligonucleotides of the mixture contain different test sequences,

(ii) adding a test molecule to be screened to a test reaction composed of (a) said DNA binding protein, and (b) said duplex DNA test oligonucleotide mixture,

(iii) incubating the molecule in the test reaction for a period sufficient to permit binding of the molecule being tested to test sequences in the duplex DNA,

(iv) separating test oligonucleotides from test oligonucleotides bound to binding protein,

(v) amplifying the separated test oligonucleotides,

(vi) repeating steps (ii) to (v),

(vii) isolating the amplified test oligonucleotides,

(viii) sequencing the isolated test oligonucleotides.

33. The method of claim 32, where said test sequences are selected from the group of 256 possible four base sequences composed of A, G, C and T.

34. The method of claim 32, where said constructing includes selecting test sequences from the sequences presented as SEQ ID NO:1 to SEQ ID NO:600.

35. The method of claim 32, where in constructing the mixture of test oligonucleotides, said adjacent screening and test sequences are flanked by primer sequences.

36. The method of claim 35, wherein said amplifying is carried out by successively repeating the steps of (a) denaturing the duplex test oligonucleotides to produce single-strand fragments, (b) hybridizing the single strands with primers, complementary to the primer sequences in the oligonucleotides, to form strand/primer complexes, (c) generating double-strand fragments from the strand/primer complexes in the presence of DNA polymerase and all four deoxyribonucleotides, and (d) repeating steps (a) to (c) until a desired degree of amplification has been achieved.

37. The method of claim 32, wherein said amplifying is carried out by cloning the separated test oligonucleotides into a vector, passaging vectors carrying the test oligonucleotides in appropriate host cells, culturing the host, isolating the vectors, and obtaining the test oligonucleotides from the vectors.

38. The method of claim 32, where said isolating is accomplished by cloning the amplified test oligonucleotides into a cloning vector.

39. The method of claim 32, where said separating is accomplished by passing the test reaction through a filter, where said filter is capable of capturing

DNA:protein complexes but not DNA that is free of protein.

40. The method of claim 32, where the DNA screening sequence is from the HSV origin of replication and the binding protein is UL9.

41. A method of screening for molecules capable of binding to a selected test sequence in a duplex DNA, comprising

(i) constructing a duplex DNA test oligonucleotide having a screening sequence adjacent a selected test sequence, where a DNA binding protein is effective to bind to said screening sequence with a binding affinity that is substantially independent of such test sequence, but where DNA protein binding to the screening sequence is sensitive to binding of test molecules to such test sequence,

(ii) adding a test molecule to be screened to a test system composed of (a) said DNA binding protein, and (b) said duplex DNA test oligonucleotide having said screening and test sequences adjacent one another,

(iii) incubating the molecule in the test system for a period sufficient to permit binding of the molecule being tested to the test sequence in the duplex DNA, and

(iv) comparing the amount of binding protein bound to the duplex DNA before and after said adding.

42. The method of claim 41, where said test sequence is selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:600.

43. The method of claim 41, where the DNA screening sequence is from the HSV origin of replication and the binding protein is UL9.

44. The method of claim 43, wherein the DNA screening sequence is selected from the group consisting of SEQ ID NO:601, SEQ ID NO:602, SEQ ID NO:615, AND SEQ ID NO:641.

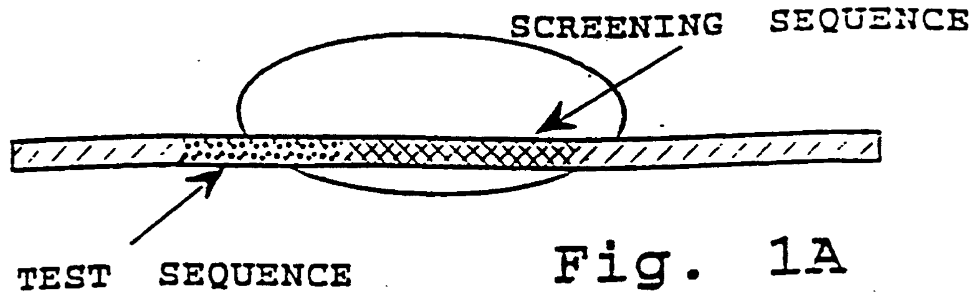


Fig. 1A

Fig. 1B

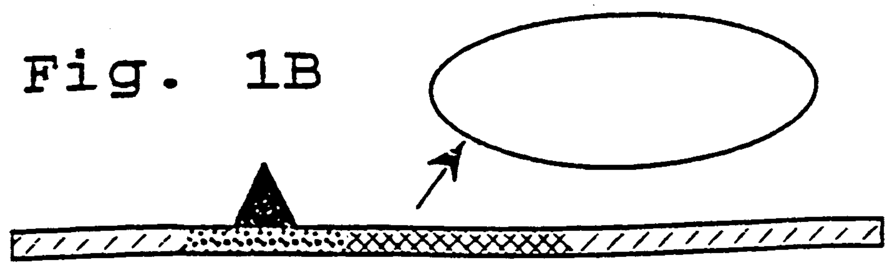
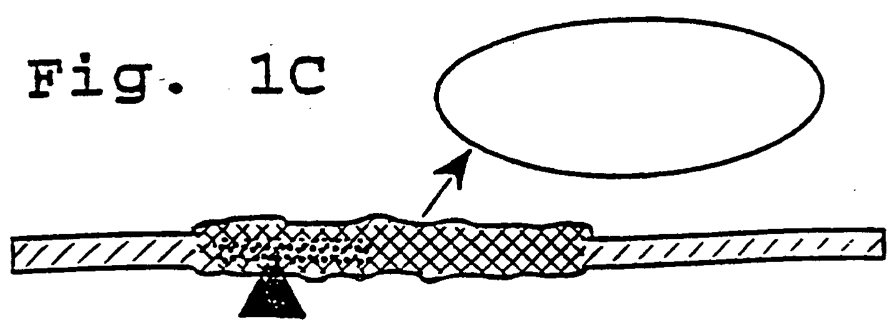


Fig. 1C



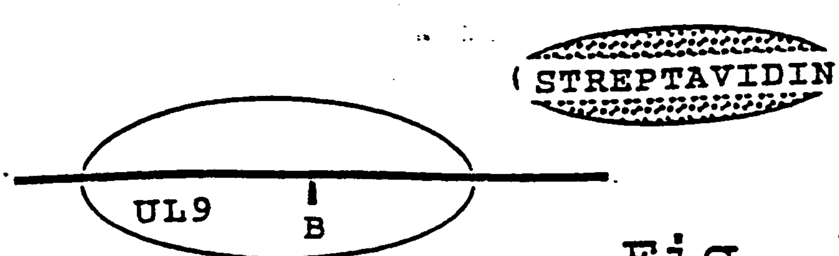


Fig. 3

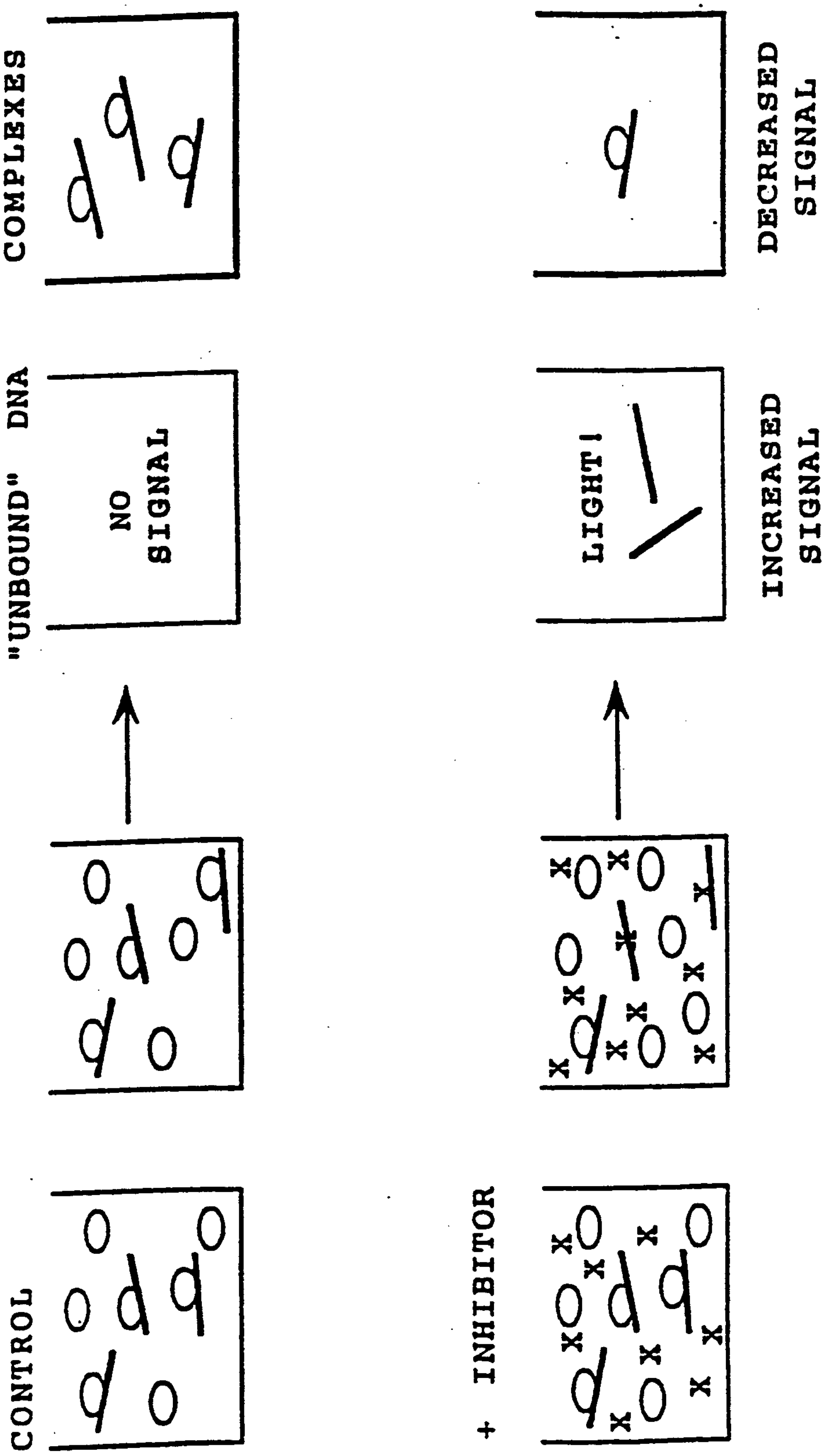

CONTROL
+ INHIBITOR
CAPTURE "UNBOUND" DNA
NO SIGNAL
LIGHT!
INCREASED SIGNAL
CAPTURE DNA:PROTEIN COMPLEXES
DECREASED SIGNAL

Fig. 2

```
                          10
                 1234567891 1
5' AAGTGAGAATTCGAAGCGTTCGCACTTCGTCCCAAT 3'
                             GAAGCAGGGTTA 5'
```

+ BIOTIN-11-dUTP
+ KLENOW ENZYME

```
5' AAGTGAGAATTCGAAGCGTTCGCACTTCGTCCCAAT 3'
                            UGAAGCAGGGTTA 5'
                            B
```

PURIFY, THEN ADD
dNTPs + KLENOW

```
5' AAGTGAGAATTCGAAGCGTTCGCACTTCGTCCCAAT 3'
3' TTCACTCTTAAGCTTCGCAAGCGUGAAGCAGGGTTA 5'
                            B
```

PURIFY, THEN ADD
DIG-11-dUTP +
TERMINAL TRANSFERASE

```
                                         DDD
   5' AAGTGAGAATTCGAAGCGTTCGCACTTCGTCCCAATUUU 3'
3'UUUTTCACTCTTAAGCTTCGCAAGCGUGAAGCAGGGTTA 5'
DDD                            B
```

PURIFY

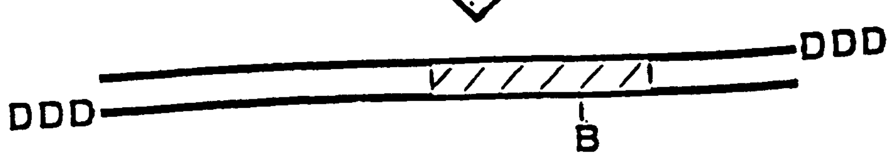


Fig. 4

	Test Sequence:	Screening Sequence:	Test Sequence
UL9Z1	5'-GCGCGCGCG (Z-DNA)	CGTTCGCACTT	CCGCCGCCGG-3'
UL9Z2	5'-GGCGCCGGC	CGTTCGCACTT	CGCGCGCGCG (Z-DNA) -3'
UL9 CCCG	5'-GGCCCGCCC	CGTTCGCACTT	CCCGCCCCGG-3'
UL9 GGGC	5'-GGCGGGCGC	CGTTCGCACTT	GGGCGGGCGG-3'
UL9 ATAT	5'-GGATATATA	CGTTCGCACTT	TAATTATTGG-3'
UL9 polyA	5'-GGAAAAAAA	CGTTCGCACTT	AAAAAAAAGG-3'
UL9 polyT	5'-GGTTTTTTT	CGTTCGCACTT	TTTTTTTTGG-3'
UL9 GCAC	5'-GGACGCACG	CGTTCGCACTT	GCAGCAGCGG-3'
ATori-1	5'-GCGTATATAT	CGTTCGCACTT	CGTCCCAAT-3'
oriEco2	5'-GGCGAATTCGA	CGTTCGCACTT	CGTCCCAAT-3'
oriEco3	5'-GGCGAATTCGAT	CGTTCGCACTT	CGTCCCAAT-3'

Fig. 5

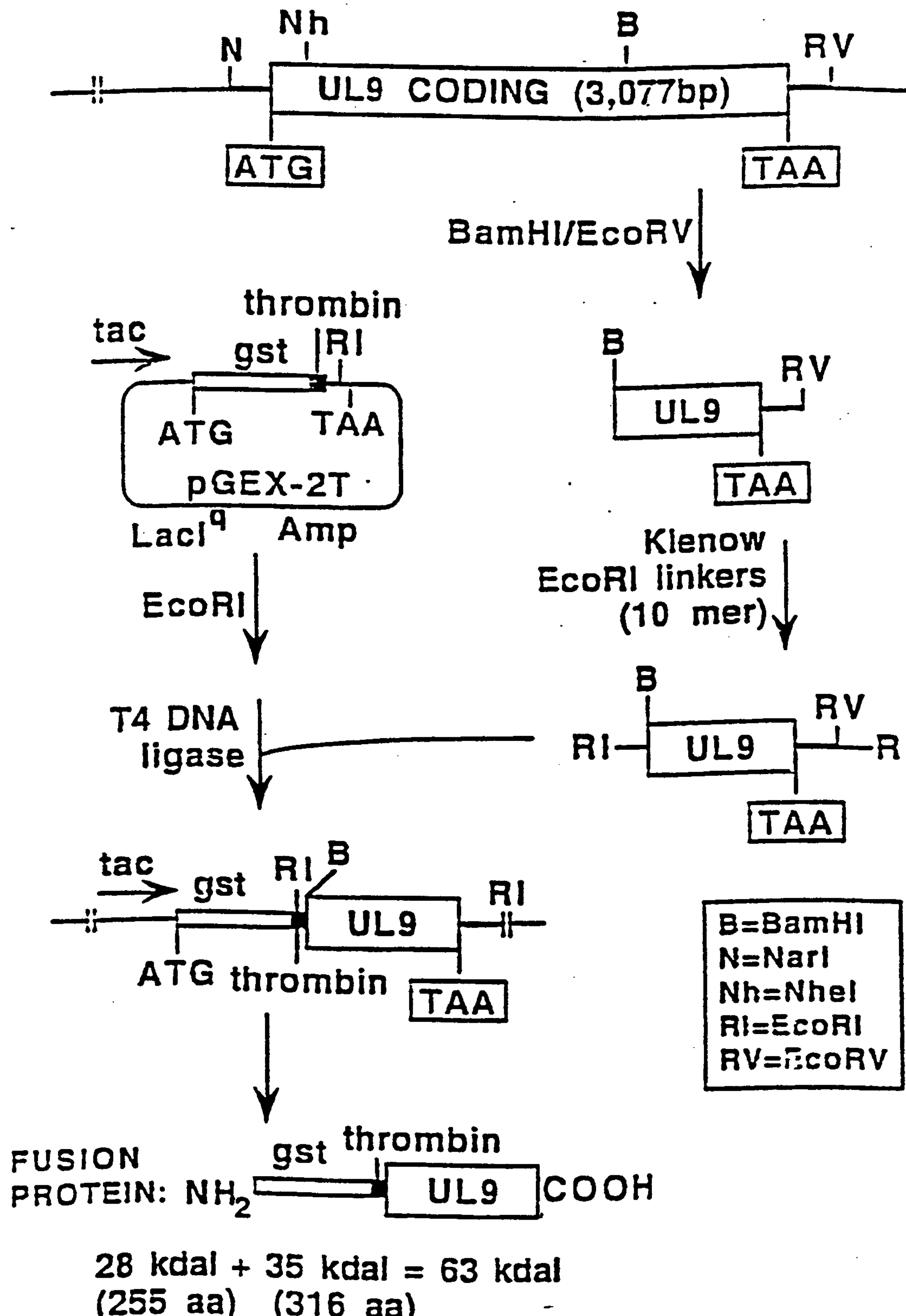

Nh
B
N
RV
UL9 CODING (3,077bp)
ATG
TAA
BamHI/EcoRV
thrombin
tac
gst
RI
B
RV
UL9
ATG
TAA
pGEX-2T
TAA
LacI^q
Amp
Klenow
EcoRI linkers
(10 mer)
EcoRI
T4 DNA
ligase
B
RV
RI
UL9
RI
TAA
tac
RI
B
gst
RI
UL9
ATG thrombin
TAA
B=BamHI
N=NarI
Nh=NheI
RI=EcoRI
RV=EcoRV
FUSION
PROTEIN: NH2
gst
thrombin
UL9
COOH
28 kdal + 35 kdal = 63 kdal
(255 aa) (316 aa)

Fig. 6

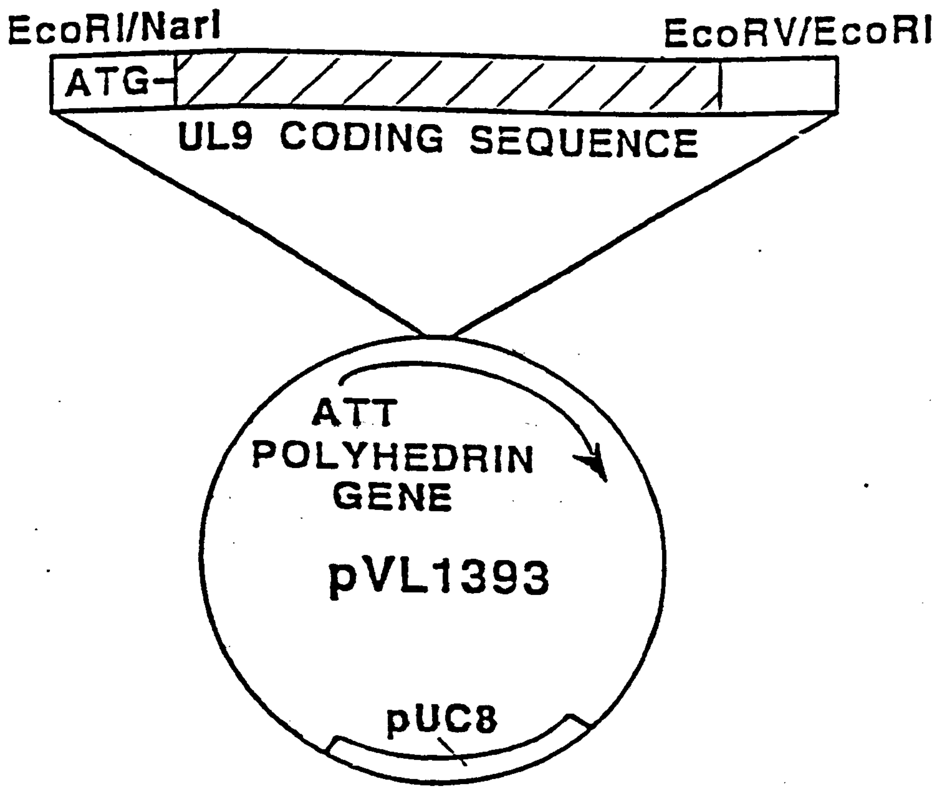
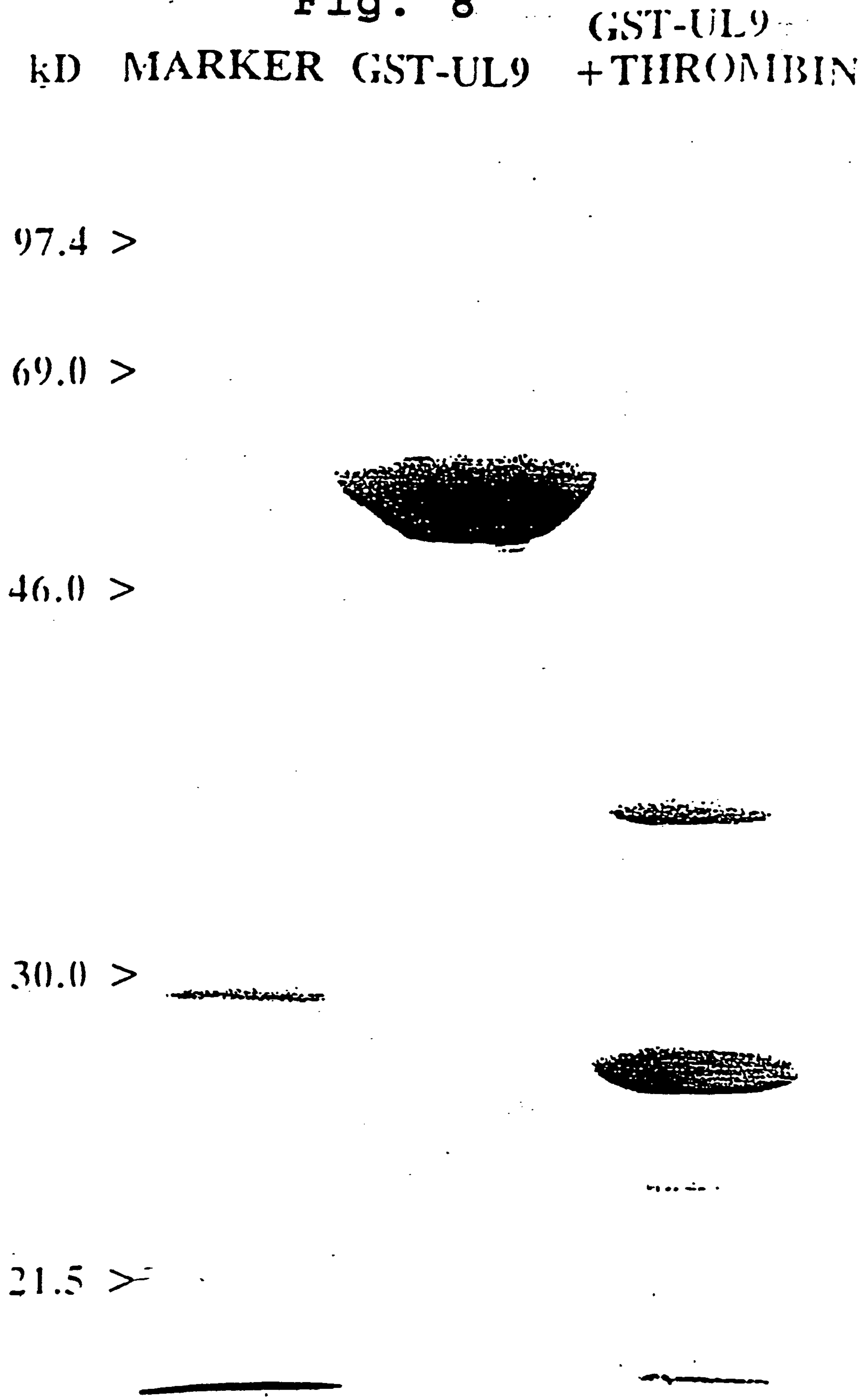

EcoRI/NarI
EcoRV/EcoRI
ATG-
UL9 CODING SEQUENCE
ATT
POLYHEDRIN
GENE
pVL1393
pUC8

Fig. 7

Fig. 8



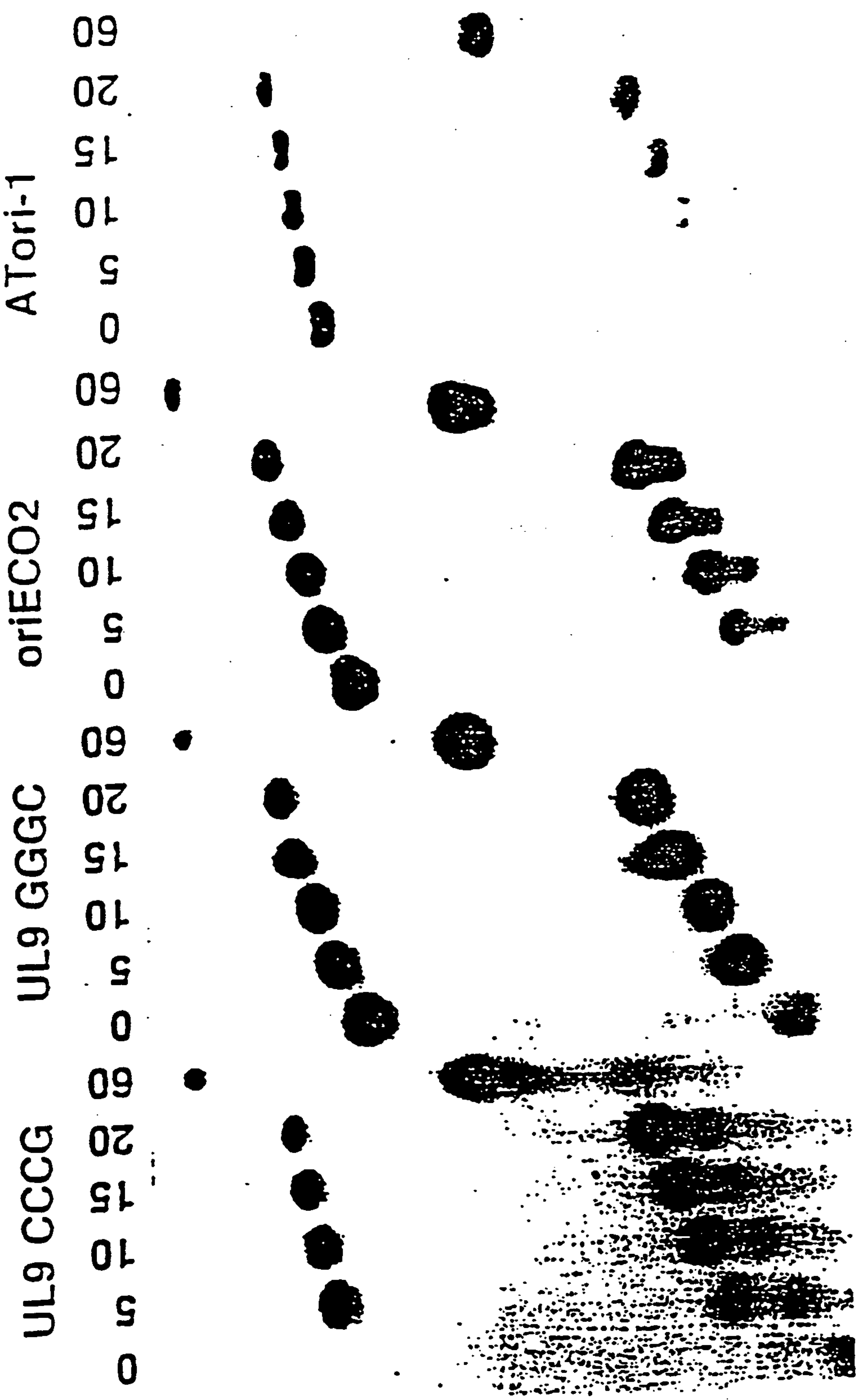

UL9 CCCG
0
5
10
15
20
60
UL9 GGGC
0
5
10
15
20
60
oriECO2
0
5
10
15
20
60
ATori-1
0
5
10
15
20
60

Fig. 9

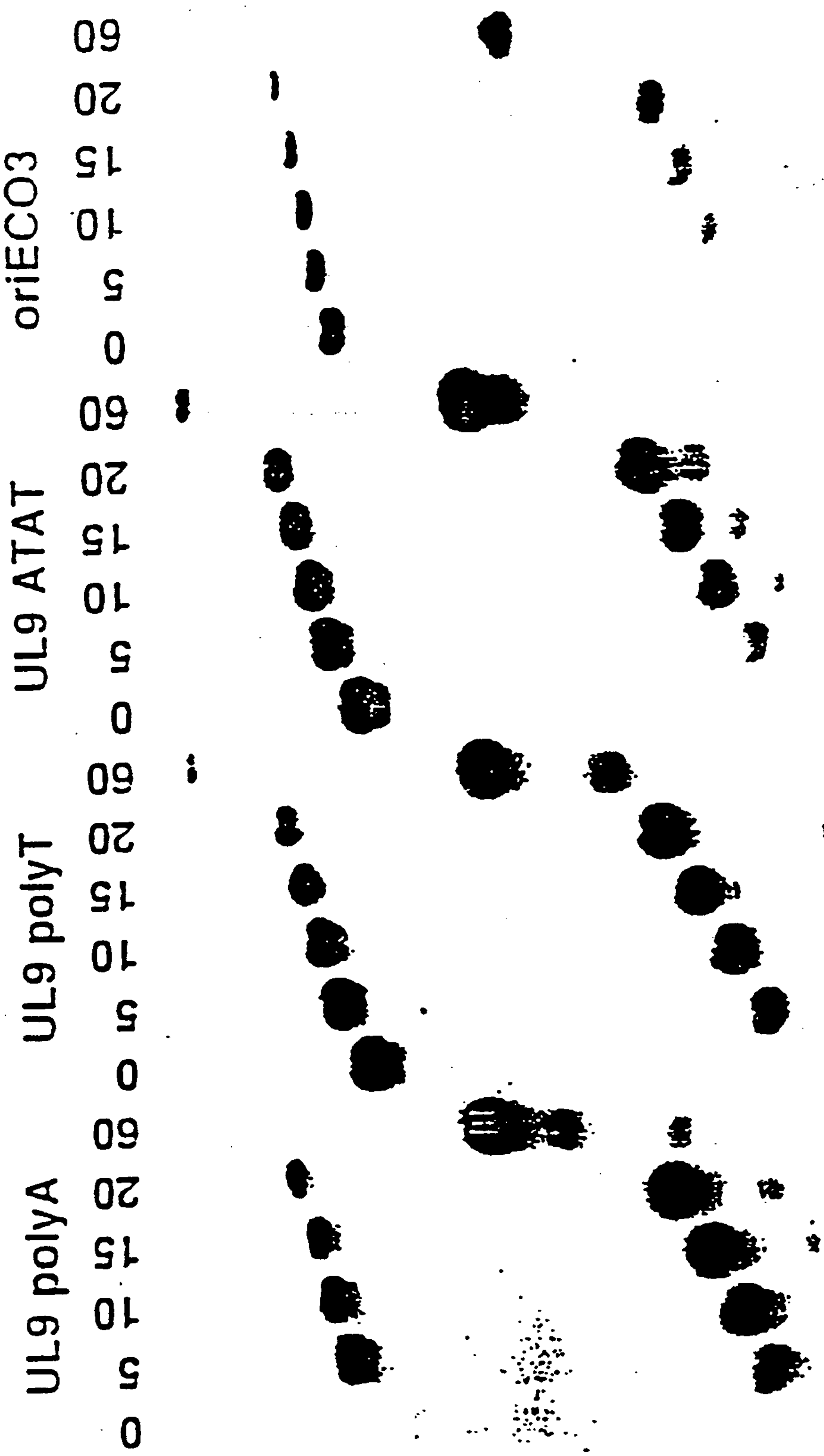

UL9 polyA
0
5
10
15
20
60
UL9 polyT
0
5
10
15
20
60
UL9 ATAT
0
5
10
15
20
60
oriECO3
0
5
10
15
20
60

Fig. 9 (con't)

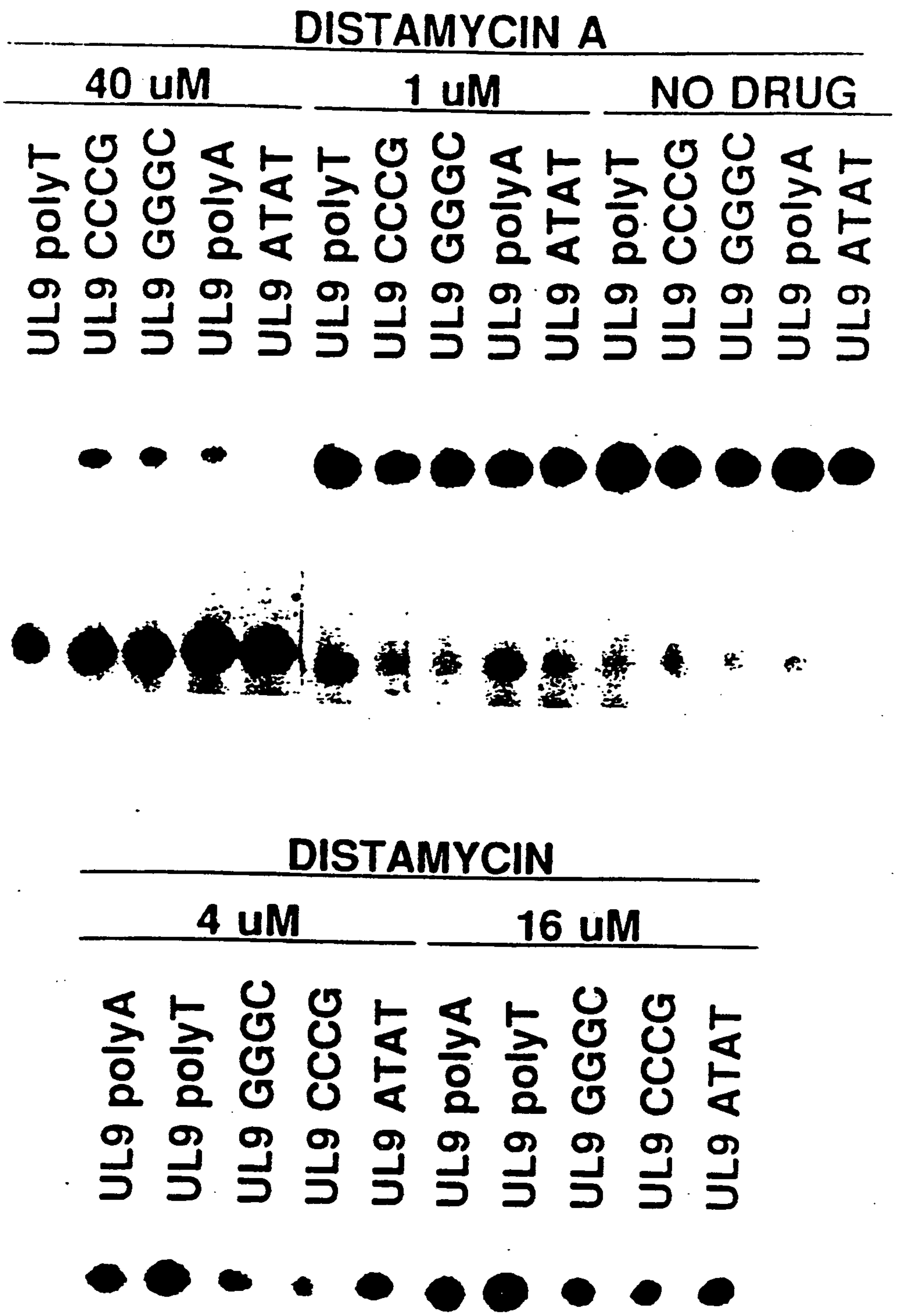

DISTAMYCIN A
40 uM
1 uM
NO DRUG
UL9 polyT
UL9 CCCG
UL9 GGGC
UL9 polyA
UL9 ATAT
UL9 polyT
UL9 CCCG
UL9 GGGC
UL9 polyA
UL9 ATAT
UL9 polyT
UL9 CCCG
UL9 GGGC
UL9 polyA
UL9 ATAT
DISTAMYCIN
4 uM
16 uM
UL9 polyA
UL9 polyT
UL9 GGGC
UL9 CCCG
UL9 ATAT
UL9 polyA
UL9 polyT
UL9 GGGC
UL9 CCCG
UL9 ATAT

Fig. 10A

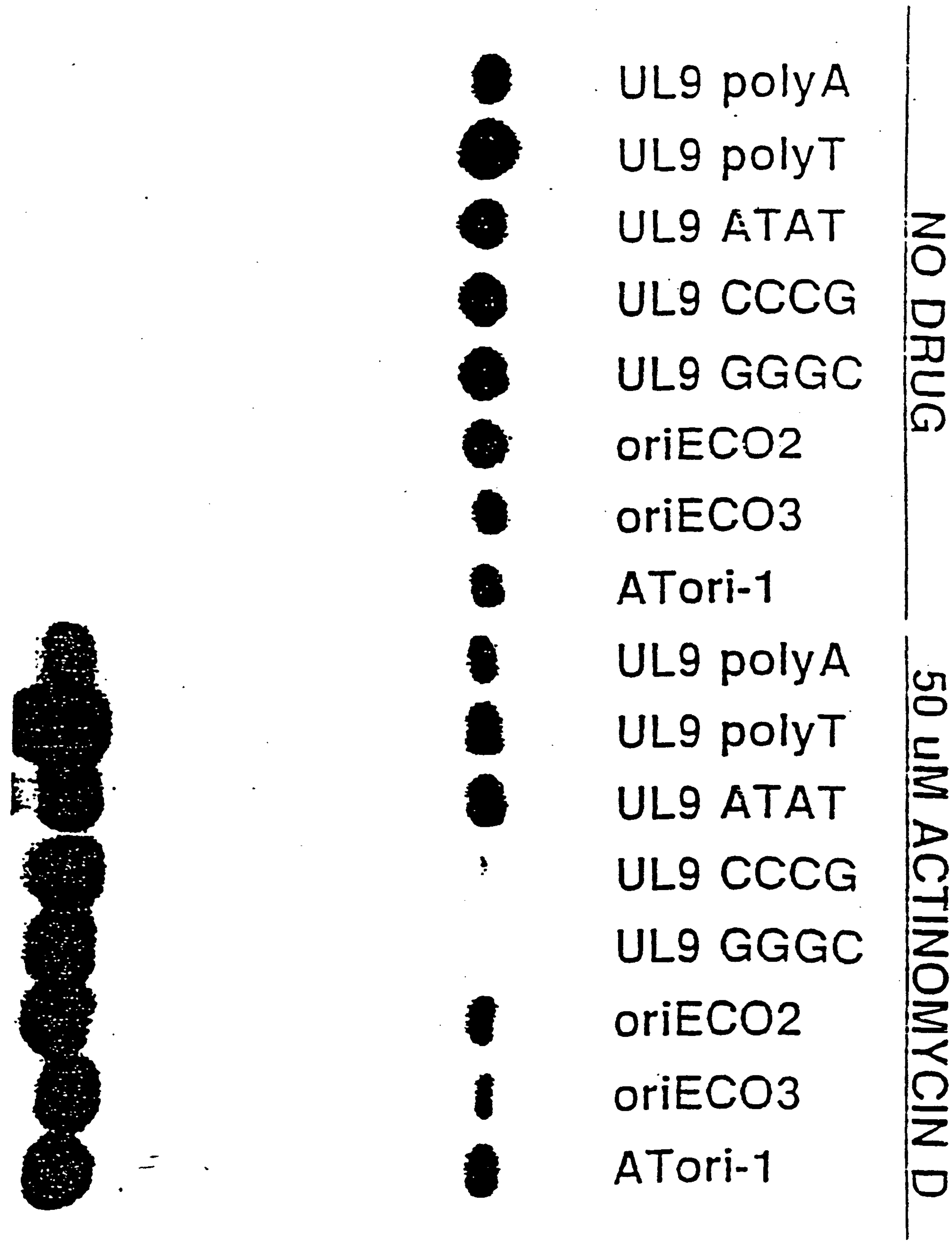

UL9 polyA
UL9 polyT
UL9 ATAT
UL9 CCCG
UL9 GGGC
oriECO2
oriECO3
ATori-1
NO DRUG
UL9 polyA
UL9 polyT
UL9 ATAT
UL9 CCCG
UL9 GGGC
oriECO2
oriECO3
ATori-1
50 uM ACTINOMYCIN D

Fig. 10B

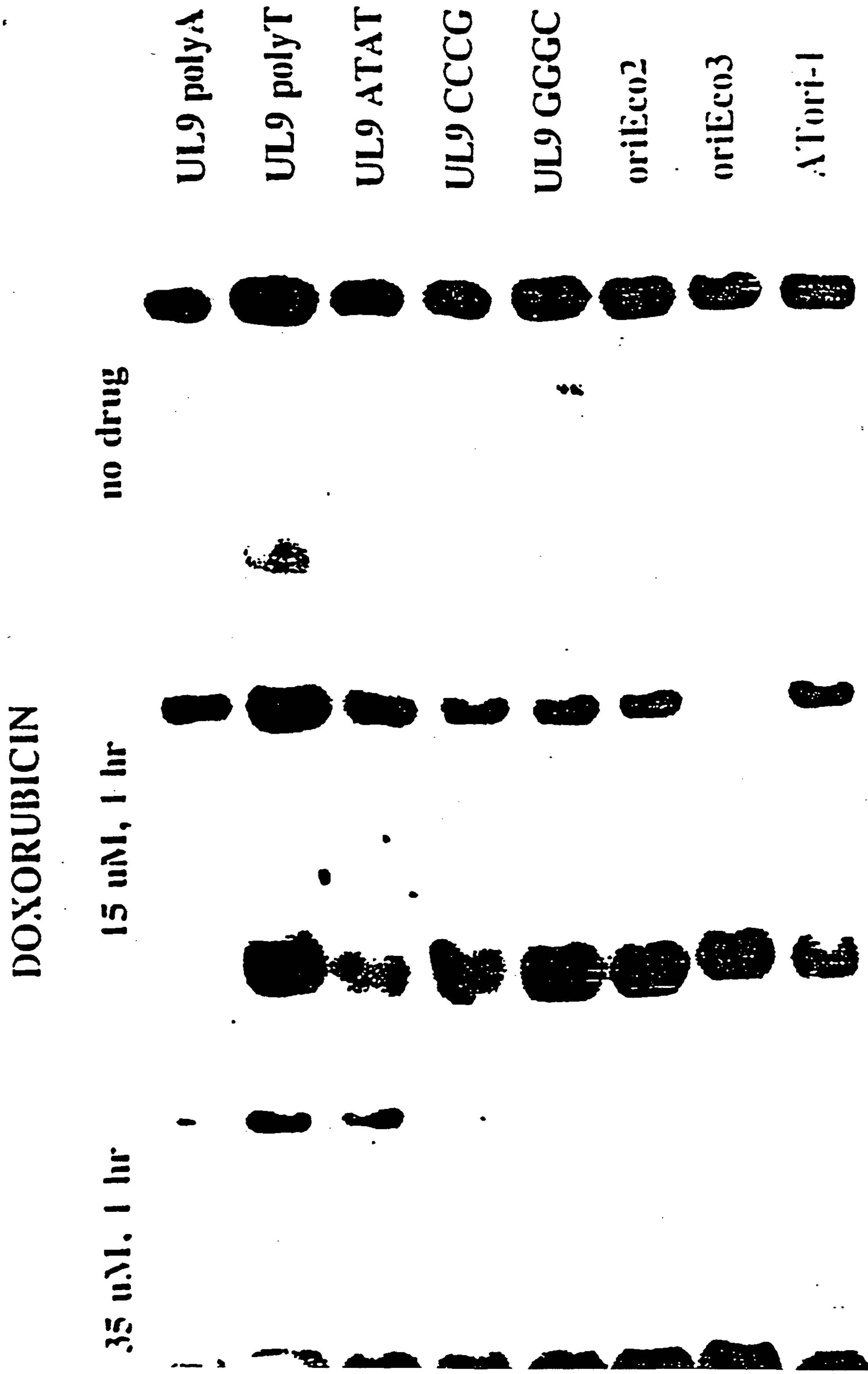

UL9 polyA
UL9 polyT
UL9 ATAT
UL9 CCCG
UL9 GGGC
oriEco2
oriEco3
ATori-1
no drug
DOXORUBICIN
15 uM, 1 hr
35 uM, 1 hr

Fig. 10C

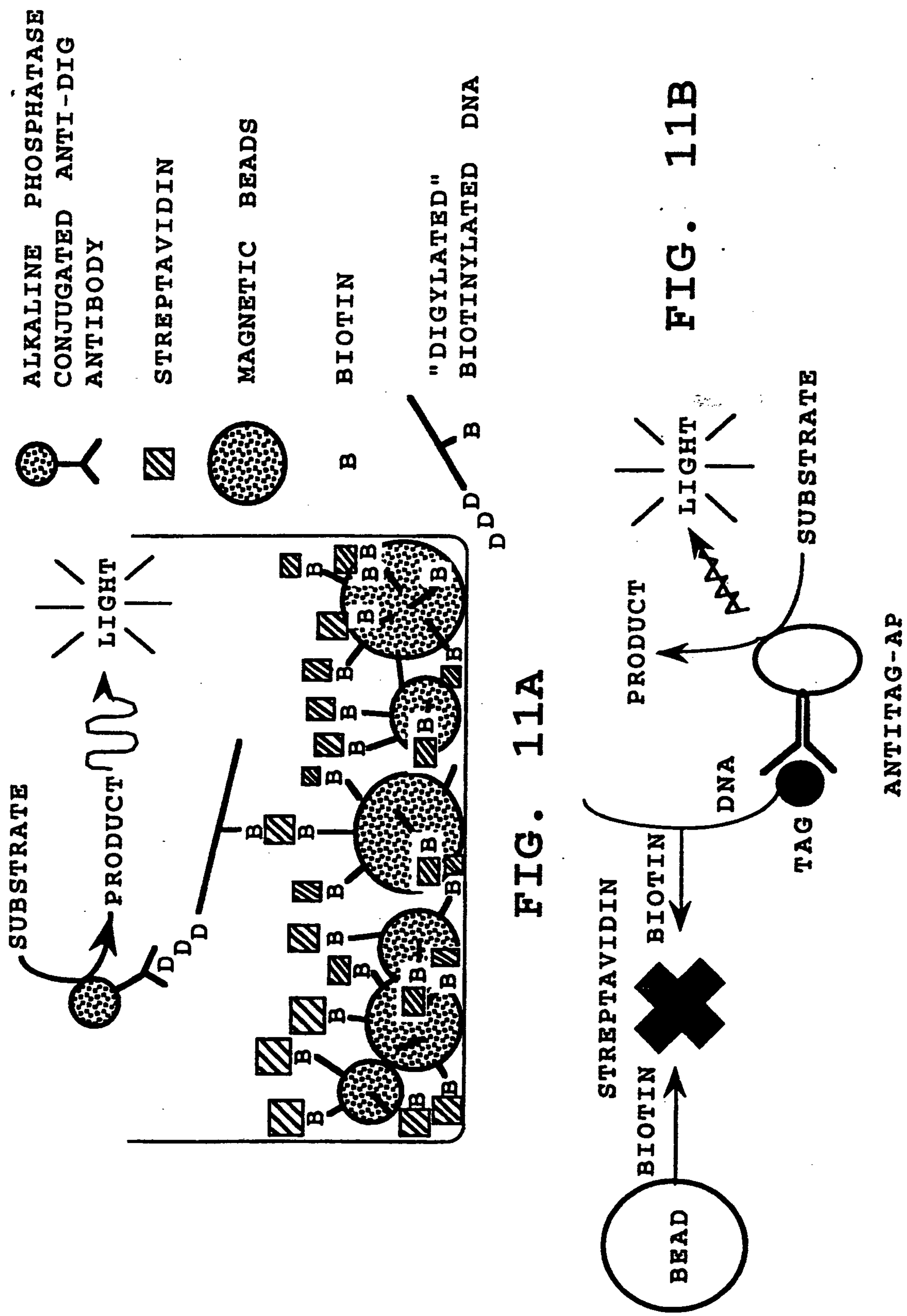


FIG. 11A

FIG. 11B

Table II. Demonstration Assay Test Matrix

Sequence		Test Mixtures 1	2	3	4	5	6	7	8
AGCTTTCGCACTTAGCT	-	+	+	-	-	-	-	-	-
AGCATTCGCACTTAGCA	-	+	-	-	+	+	-	-	-
AGCCTTCGCACTTAGCC	-	+	-	-	-	-	-	-	+
AGCGTTCGCACTTAGCG	-	+	-	-	-	-	-	-	-
TGCTTTCGCACTTTGCT	-	+	-	-	-	-	-	+	-
TGCATTCGCACTTTGCA	-	+	-	-	+	+	-	+	-
TGCCTTCGCACTTTGCC	-	+	-	-	-	-	-	+	+
TGCGTTCGCACTTTGCG	-	+	-	-	-	-	-	+	-
:	:	:	:	:	:	:	:	:	:
:	:	:	:	:	:	:	:		
CCATTTCGCACTTCCAT	-	+	-	-	+	-	-	-	+
CCCTTTCGCACTTCCCT	-	+	-	-	-	-	-	+	+
CCGTTTCGCACTTCCGT	-	+	-	-	-	-	-	-	+
CCTTTTCGCACTTCCTT	-	+	-	-	-	-	-	+	+
:	:	:	:	:	:	:	:	:	:

Fig. 12

SEQUENCE									
AAAA	001	ATCA	053	CGGA	105	GCTA	157	TCAA	209
AAAC	002	ATCC	054	CGCG	106	GCTC	158	TCAC	210
AAAG	003	ATCG	055	CGGG	107	GCTG	159	TCAG	211
AAAT	004	ATCT	056	CGGT	108	GCTT	160	TCAT	212
AACA	005	ATGA	057	CGTA	109	GGAA	161	TCCA	213
AACC	006	ATGC	058	CGTC	110	GGAC	162	TCCC	214
AACG	007	ATGG	059	CGTG	111	GGAG	163	TCCG	215
AACT	008	ATGT	060	CGTT	112	GGAT	164	TCCT	216
AAGA	009	ATTA	061	CTAA	113	GGCA	165	TCGA	217
AAGC	010	ATTC	062	CTAC	114	GGCC	166	TCGC	218
AAGC	011	ATTG	063	CTAG	115	GGCG	167	TCGG	219
AAGT	012	ATTT	064	CTAT	116	GGCT	168	TCGT	220
AATA	013	CAAA	065	CTCA	117	GGGA	169	TCTA	221
AATC	014	CAAC	066	CTCC	118	GGGC	170	TCTC	222
AATG	015	CAAG	067	CTCG	119	GGGG	171	TCTG	223
AATT	016	CAAT	068	CTCT	120	GGGT	172	TCTT	224
ACAA	017	CACA	069	CTGA	121	GGTA	173	TGAA	225
ACAC	018	CACC	070	CTGC	122	GGTC	174	TGAC	226
ACAG	019	CACG	071	CTGG	123	GGTG	175	TGAG	227
ACAT	020	CACT	072	CTGT	124	GGTT	176	TGAT	228
ACCA	021	CAGA	073	CTTA	125	GTAA	177	TGCA	229
ACCC	022	CAGC	074	CTTC	126	GTAC	178	TGCC	230
ACCG	023	CAGG	075	CTTG	127	GTAG	179	TGCG	231
ACCT	024	CAGT	076	CTTT	128	GTAT	180	TGCT	232
ACGA	025	CATA	077	GAAA	129	GTCA	181	TGGA	233
ACGC	026	CATC	078	GAAC	130	GTCC	182	TGGC	234
ACGC	027	CATG	079	GAAG	131	GTCG	183	TGGG	235
ACGT	028	CATT	080	GAAT	132	GTCT	184	TGGT	236
ACTA	029	CCAA	081	GACA	133	GTGA	185	TGTA	237
ACTC	030	CCAC	082	GACC	134	GTGC	186	TGTC	238
ACTG	031	CCAG	083	GACG	135	GTGG	187	TGTG	239

Fig 13

ACTT	032	CCAT	084	GACT	136	GTGT	188	TGTT	240
AGAA	033	CCCA	085	GAGA	137	GTTA	189	TTAA	241
AGAC	034	CCCC	086	GAGC	138	GTTC	190	TTAC	242
AGAG	035	CCCG	087	GAGG	139	GTTG	191	TTAG	243
AGAT	036	CCCT	088	GAGT	140	GTTT	192	TTAT	244
AGCA	037	CCGA	089	GATA	141	TAAA	193	TTCA	245
AGCC	038	CCGC	090	GATC	142	TAAC	194	TTCC	246
AGCG	039	CCGG	091	GATG	143	TAAG	195	TTCG	247
AGCT	040	CCGT	092	GATT	144	TAAT	196	TTCT	248
AGGA	041	CCTA	093	GCAA	145	TACA	197	TTGA	249
AGGC	042	CCTC	094	GCAC	146	TACC	198	TTGC	250
AGGG	043	CCTG	095	GCAG	147	TACG	199	TTGG	251
AGGT	044	CCTT	096	GCAT	148	TACT	200	TTGT	252
AGTA	045	CGAA	097	GCCA	149	TAGA	201	TTTA	253
AGTC	046	CGAC	098	GCCC	150	TAGC	202	TTTC	254
AGTG	047	CGAG	099	GCCG	151	TAGG	203	TTTG	255
AGTT	048	CGAT	100	GCCT	152	TAGT	204	TTTT	256
ATAA	049	CGCA	101	GCGC	154	TATA	205		
ATAC	050	CGCC	102	GCGA	153	TATC	206		
ATAG	051	CGCG	103	GCGG	155	TATG	207		
TATA	052	CGCT	104	GCGT	156	TATT	208		

Fig. 13 (con't)

GATC	AGTC	TAGC	CGAT
GACT	AGCT	TACG	CGTA
GTCA	ATCG	TGCA	CATG
GTAC	ATGC	TGAC	CAGT
GCTA	ACTG	TCAG	CTAG
GCAT	ACGT	TCGA	CTGA

Fig. 14A

Screening
Sequence

GCGTANXXXXCGTTCGCACTTXXXXCTTCGTCCCAAT
CGCATNXXXXGCAAGCGTGAAXXXXGAAGCAGGGTTA

Test Site   Test Site

Fig. 14B

Sort by average rank:

rank:	oligo	seqenc	% r918A	rank	%r918B	rank	%r1022A	rank	%r1022B	rank	ave r%	ave rank
1	246	TTCC	47	14	44	14	41	4	27	3	40	9
2	242	TTAC	49	19	47	19	55	17	46	15	49	18
3	198	TACC	57	43	48	22	50	7	39	10	48	21
4	206	TATC	50	20	46	18	54	16	59	45	52	25
5	7	AACG	56	38	56	52	48	6	34	4	49	25
6	247	TTCG	56	36	49	26	58	20	54	34	54	29
7	254	TTTC	51	21	35	4	66	46	63	59	54	33
8	27	ACGG	55	30	55	49	63	33	51	24	56	34
9	202	TAGC	65	74	46	16	67	52	18	1	49	36
10	243	TTAG	61	57	53	43	58	21	51	23	56	36
11	251	TTGG	61	59	44	13	60	23	62	53	57	37
12	194	TAAC	66	83	51	35	45	5	52	30	54	38
13	3	AAAG	60	54	58	60	65	37	42	12	56	41
14	6	AACC	70	101	58	51	51	9	34	5	53	42
15	199	TACG	66	82	53	45	51	8	53	31	56	42
16	66	CAAC	54	27	58	59	70	64	52	29	59	45
17	34	AGAC	55	32	52	41	63	32	67	75	59	45
18	2	AAAC	72	117	50	31	52	12	51	25	58	46
19	54	ATCC	55	29	58	61	75	93	36	7	56	48
20	11	AAGG	68	90	59	62	60	26	48	18	59	49
21	39	AGCG	49	18	53	44	80	138	39	8	55	52
22	38	AGCC	55	34	46	17	80	133	58	41	60	56
23	195	TAAG	70	105	63	72	57	19	54	32	61	57
24	248	TTCT	70	104	52	40	65	38	60	46	61	57
25	26	ACGC	58	45	49	25	78	116	59	44	61	58
26	22	ACCC	64	72	49	28	65	40	71	93	62	58
27	58	ATGC	63	67	65	77	68	53	55	37	63	59
28	43	AGGG	41	6	51	38	86	170	49	21	57	59
29	214	TCCC	68	87	62	70	65	41	58	42	63	60
30	42	AGGC	43	8	49	24	90	195	44	14	56	60
31	207	TATG	58	48	67	87	62	29	68	79	64	60
32	23	ACCG	54	25	58	57	80	134	52	26	61	61
33	51	ATAG	48	15	73	111	68	55	63	63	63	61
34	219	TCGG	62	60	74	114	65	36	61	48	65	65
35	46	AGTC	18	2	42	9	74	90	80	160	54	65
36	249	TTGA	71	109	51	36	71	71	62	55	64	68
37	250	TTGC	56	35	50	30	67	49	80	161	63	69
38	119	CTCG	54	26	85	176	61	27	60	47	65	69
39	55	ATCG	56	37	84	169	66	44	52	28	64	70
40	215	TCCG	62	61	58	55	73	81	70	86	66	71
41	231	TGCG	63	66	65	79	70	63	69	83	67	-73
42	161	GGAA	43	10	72	107	79	128	67	73	65	80
43	255	TTTG	59	48	51	37	64	35	87	199	65	80
44	14	AATC	71	112	50	33	82	152	52	27	64	81
45	238	TGTC	72	119	64	74	65	42	70	89	68	81
46	35	AGAG	56	41	55	47	87	184	62	54	65	82
47	241	TTAA	76	137	84	170	51	10	41	11	63	82
48	18	ACAC	66	80	50	29	97	216	36	6	62	83
49	47	AGTG	51	22	42	10	105	231	65	68	66	83
50	245	TTCA	81	157	68	84	60	25	65	69	68	84
51	205	TATA	70	102	68	85	71	70	69	82	69	85
52	210	TCAC	65	75	45	15	21	2	*57.3	250	43	86
53	36	AGAT	70	100	43	11	102	224	39	9	64	86
54	244	TTAT	80	149	62	69	61	28	71	99	69	86
55	234	TGGC	56	40	61	68	82	150	70	88	67	87
56	256	TTTT	54	28	58	58	71	67	86	195	67	87
57	193	TAAA	74	124	74	117	68	54	63	61	70	89
58	203	TAGG	84	178	59	63	62	30	70	90	69	90
59	63	ATTG	60	51	78	122	80	137	63	56	70	92
60	227	TGAG	75	126	39	6	71	73	81	164	67	92
61	116	CTAT	73	121	74	118	65	43	70	87	71	92
62	217	TCGA	60	53	85	175	69	59	71	95	72	96
63	59	ATGG	62	65	82	150	79	130	56	39	70	96
64	62	ATTC	64	69	71	102	93	203	43	13	68	97
65	185	GTGA	44	12	62	71	76	105	87	201	67	97
66	61	ATTA	77	140	87	179	67	50	49	22	70	98
67	50	ATAC	54	24	71	97	105	232	56	38	71	98
68	235	TGGG	60	52	71	104	78	115	76	121	71	98
69	166	GGCC	80	148	24	1	77	114	77	133	65	99

Fig. 15

70	107	CGGG	65	78	100	218	67	51	61	50	73	99
71	232	TGCT	69	97	49	27	73	79	87	198	70	100
72	158	GCTC	33	3	66	83	71	72	131	243	75	100
73	19	ACAG	69	95	65	75	91	197	54	36	70	101
74	10	AAGC	80	151	70	93	73	82	70	85	73	103
75	208	TATT	70	106	72	105	75	97	73	105	72	103
76	1	AAAA	83	171	79	137	67	47	63	58	73	103
77	182	GTCC	76	135	60	66	70	65	79	150	71	104
78	157	GCTA	49	16	97	209	77	111	68	61	73	104
79	191	GTTG	110	244	43	12	76	102	83	60	73	105
80	172	GGGT	39	4	58	58	89	192	81	168	67	105
81	150	GCCC	58	44	80	142	86	172	63	62	72	105
82	15	AATG	68	88	70	94	108	237	22	2	67	105
83	196	TAAT	94	220	67	86	66	45	67	74	74	106
84	187	GTGG	44	11	100	220	69	58	78	140	73	107
85	184	GTCT	62	82	48	23	77	109	100	236	72	108
86	115	CTAG	70	98	94	203	60	24	73	106	74	108
87	120	CTCT	61	56	114	246	59	22	73	107	77	108
88	167	GGCG	65	73	81	145	80	135	68	80	73	108
89	239	TGTG	72	114	37	5	81	144	82	171	68	109
90	233	TGGA	66	84	65	78	76	106	82	170	72	110
91	52	ATAT	84	70	94	199	78	123	61	49	74	110
92	220	TCGT	73	122	47	21	83	157	78	142	70	111
93	183	GTCG	66	81	83	158	69	57	79	146	74	111
94	25	ACGA	60	55	74	116	100	221	62	52	74	111
95	226	TGAC	71	111	73	110	71	69	80	156	74	112
96	33	AGAA	55	33	82	155	122	246	48	16	77	113
97	114	CTAC	61	58	77	125	54	15	78.17	253	64	113
98	211	TCAG	75	130	70	95	75	100	76	126	74	113
99	104	CGCT	69	93	92	194	64	34	77	131	75	113
100	142	GATC	64	68	33	3	84	160	92	224	68	114
101	230	TGCC	73	123	60	67	73	77	85	188	73	114
102	209	TCAA	72	115	69	91	84	158	71	92	74	114
103	162	GGAC	41	7	83	157	67	48	149	244	85	114
104	87	CAAG	86	184	66	82	86	174	49	19	72	115
105	252	TTGT	82	162	56	50	77	113	78	136	73	115
106	222	TCTC	89	94	77	127	84	183	68	77	75	115
107	174	GGTC	65	76	107	237	54	14	77	134	76	115
108	30	ACTC	73	120	65	81	131	250	48	17	79	117
109	71	CACG	13	1	83	162	88	186	76	122	65	118
110	45	AGTA	60	50	77	128	106	234	64	66	77	119
111	201	TAGA	94	216	77	129	72	75	63	57	76	119
112	29	ACTA	81	153	42	8	131	249	64	67	79	119
113	24	ACCT	56	39	93	195	95	210	54	35	75	120
114	31	ACTG	68	89	73	109	112	240	58	43	78	120
115	175	GGTG	71	110	94	200	55	18	80	158	75	122
116	131	GAAG	69	91	71	100	78	120	83	175	75	122
117	229	TGCA	76	136	83	163	78	118	67	72	76	122
118	163	GGAG	49	17	106	234	69	60	85	184	77	124
119	90	CCGC	83	172	82	148	69	58	75	119	77	124
120	253	TTTA	75	128	72	108	74	85	84	180	76	125
121	118	CTCC	78	142	57	54	75	98	89	207	75	125
122	151	GCCG	52	23	110	243	84	164	67	71	78	125
123	155	GCGG	62	64	69	92	108	236	75	114	79	127
124	221	TCTA	75	134	71	98	82	153	77	129	76	129
125	179	GTAG	141	250	59	64	75	95	73	108	87	129
126	122	CTGC	89	200	76	121	74	91	74	109	78	130
127	197	TACA	87	192	88	183	71	68	68	78	79	130
128	143	GATG	62	63	57	53	105	229	84	181	77	132
129	170	GGGC	43	9	92	190	78	119	89	209	75	132
130	44	AGGT	65	77	69	90	124	247	75	116	83	133
131	57	ATGA	72	118	88	181	92	201	57	40	77	135
132	13	AATA	86	186	106	235	14	1	76	120	70	136
133	130	GAAC	90	205	65	76	80	136	76	125	78	136
134	236	TGGT	75	132	60	65	78	122	92	225	78	136
135	216	TCCT	83	169	71	99	82	149	77	130	78	137
136	41	AGGA	81	158	51	39	151	253	71	97	89	137
137	237	TGTA	82	166	74	115	74	89	83	178	78	137
138	9	AAGA	87	191	78	133	82	154	67	70	79	137
139	218	TCGC	72	113	78	132	75	96	90	211	79	138
140	56	ATCT	75	133	81	146	89	189	69	84	79	138

Fig. 15(con't)

141	108	CGGT	64	71	94	201	73	78	88	205	80	139
142	98	CGAC	94	219	84	188	54	13	80	159	78	140
143	145	GCAA	57	42	105	230	77	112	84	179	81	141
144	112	CGTT	80	152	82	151	78	101	81	165	80	142
145	96	CCTT	69	92	29	2	106	235	105	241	77	143
146	48	AGTT	70	107	47	20	116	243	87	200	80	143
147	171	GGGG	55	31	112	244	77	107	86	194	82	144
148	12	AAGT	76	138	89	184	102	223	54	33	80	145
149	154	GCGC	89	203	74	113	98	214	62	51	80	145
150	89	CCGA	95	222	50	32	74	88	104	239	81	145
151	240	TGTT	79	146	65	80	86	173	84	183	79	146
152	79	CATG	92	209	79	138	78	121	75	118	81	146
153	165	GGCA	60	49	105	232	72	74	95	231	83	147
154	204	TAGT	96	225	86	178	77	108	68	76	81	147
155	87	CCCG	85	182	82	152	73	80	83	174	81	147
156	200	TACT	97	230	84	167	74	86	74	110	82	148
157	132	GAAT	75	129	108	254	70	61	81	167	83	148
158	146	GCAC	59	47	115	248	87	183	75	115	84	148
159	49	ATAA	65	79	84	163	128	248	72	102	87	149
160	4	AAAT	86	183	105	231	78	117	64	65	83	149
161	70	CACC	89	199	98	207	75	99	71	98	83	151
162	110	CGTC	98	233	92	191	73	83	71	96	83	151
163	28	ACGT	83	168	55	48	146	252	78	138	90	152
164	8	AACT	81	160	83	159	94	182	77	128	81	152
165	92	CCGT	81	159	77	130	73	84	102	238	84	153
166	5	AACA	83	170	93	197	84	161	71	91	83	155
167	84	CCAT	108	242	54	46	87	177	80	155	82	155
168	190	GTTC	84	174	88	86	85	168	85	192	80	156
169	160	GCTT	44	13	89	188	92	202	92	222	79	156
170	78	CATC	92	213	83	161	79	128	76	124	83	156
171	123	CTGG	88	185	89	185	81	145	74	111	83	157
172	228	TGAT	102	240	71	101	81	146	78	143	83	158
173	135	GACG	82	164	79	135	89	191	79	147	82	159
174	149	GCCA	70	99	97	210	105	228	72	101	88	160
175	128	CTTT	79	144	77	128	85	169	88	203	82	161
176	159	GCTG	40	5	104	229	88	171	105	240	84	161
177	17	ACAA	82	167	112	245	98	213	49	20	85	161
178	225	TGAA	91	208	76	124	81	140	83	176	83	162
179	184	GGAT	67	86	100	221	82	148	85	191	84	162
180	178	GTAC	92	212	75	120	85	166	79	149	83	162
181	77	CATA	155	252	60	34	102	222	78	139	96	162
182	105	CGGA	84	173	110	242	52	11	92	223	84	162
183	53	ATCA	75	131	83	158	105	230	77	135	85	163
184	40	AGCT	75	127	71	103	104	226	87	197	84	163
185	173	GGTA	71	108	96	206	88	187	80	154	83	164
186	156	GCGT	74	125	78	123	119	245	81	162	88	164
187	88	CCCT	88	193	80	138	74	92	101	237	88	165
188	32	ACTT	69	96	82	154	134	251	81	168	92	167
189	144	GATT	67	85	80	143	100	220	91	220	85	167
190	223	TCTG	77	139	95	204	77	110	91	217	85	168
191	134	GACC	97	229	89	89	87	180	82	173	84	168
192	75	CAGG	96	228	73	108	57	182	79	153	84	168
193	91	CCGG	80	150	81	147	81	141	97	233	85	168
194	72	CACT	93	215	107	238	53	156	63	64	87	168
195	153	GCGA	72	116	100	219	111	239	72	103	89	169
196	192	GTTT	125	248	74	119	84	159	79	151	91	169
197	137	GAGA	89	201	40	7	103	225	*248.59	248	78	170
198	127	CTTG	81	156	92	193	82	151	85	185	85	171
199	93	CCTA	86	187	92	192	78	103	88	204	88	172
200	176	GGTT	117	246	70	86	81	142	88	202	89	172
201	213	TCCA	77	141	78	134	87	178	99	234	85	172
202	80	ATGT	79	145	83	160	116	242	78	141	89	172
203	125	CTTA	88	189	52	42	85	211	*79.5	254	78	174
204	188	GGCT	101	239	85	172	79	129	80	157	86	174
205	139	GAGG	92	210	94	198	85	167	76	123	87	175
206	147	GCAG	70	103	120	251	90	198	79	152	90	176
207	37	AGCA	79	143	81	144	94	207	89	210	86	176
208	101	CGCA	79	147	88	182	78	124	*65.76	252	82	176
209	224	TCTT	93	214	73	112	84	165	91	216	85	177
210	103	CGCG	91	207	116	250	62	31	91	219	90	177
211	180	GTAT	179	254	100	218	75	94	79	144	108	177

Fig. 15(con't)

212	64	ATTT	84	175	83	165	94	208		82	172	88	180
213	141	GATA	95	224	82	153	91	200		79	145	87	181
214	140	GAGT	117	245	63	73	96	215		85	189	90	181
215	169	GGGA	82	165	145	254	89	190		75	113	98	181
216	97	CGAA	153	251	101	223	24	3		798	246	269	181
217	94	CCTC	92	211	82	149	86	175		85	190	88	181
218	186	GTGC	205	255	356	256	74	87		77	127	178	181
219	82	CCAC	97	232	85	174	80	131		86	183	87	183
220	113	CTAA	85	180	109	240	70	62	*60.31		251	88	183
221	212	TCAT	89	188	77	131	89	183		91	215	87	184
222	65	CAAA	84	179	116	249	95	209		72	100	92	184
223	99	CGAG	103	241	99	215	65	39		180	245	112	185
224	102	CGCC	88	195	106	233	70	68	*35.62		249	88	186
225	76	CAGT	96	227	85	177	93	205		78	137	88	187
226	126	CTTC	81	161	90	187	81	147	*88.2		256	84	188
227	21	ACCA	85	181	99	213	113	241		75	117	93	188
228	189	GTTA	178	253	210	255	81	145		72	104	135	189
229	69	CACA	82	163	83	164	98	219		90	212	88	190
230	111	CGTG	81	155	109	239	81	139		93	227	91	190
231	138	GAGC	84	176	80	139	91	199	*171.29		247	85	190
232	100	CGAT	89	202	80	141	163	255		81	163	103	190
233	74	CAGC	95	223	94	202	78	125		90	213	89	191
234	106	CGGC	99	236	98	211	93	204		75	112	91	191
235	129	GAAA	87	190	93	196	87	185		87	196	89	192
236	181	GTCA	98	234	98	212	76	104		91	218	91	192
237	73	CAGA	97	231	102	226	98	217		71	94	92	192
238	20	ACAT	89	196	91	188	109	238		79	148	92	193
239	83	CCAG	90	204	85	171	96	212		85	186	89	193
240	152	GCCT	88	194	91	189	94	208		85	187	89	194
241	95	CCTG	89	197	85	173	87	178		99	235	90	196
242	148	GCAT	94	218	100	217	98	218		77	132	92	196
243	81	CCAA	91	208	101	224	88	188		83	177	91	199
244	177	GTAA	130	249	133	252	79	127		81	169	106	199
245	117	CTCA	81	154	101	222	89	194		95	230	91	200
246	109	CGTA	120	247	115	247	72	76		97	232	101	201
247	121	CTGA	101	238	95	205	87	181		84	182	92	202
248	16	AATT	96	226	80	140	117	244		89	206	95	204
249	86	CCCC	84	177	103	228	91	198		93	226	93	207
250	85	CCCA	99	237	102	225	83	155		115	242	100	215
251	188	GTGT	217	256	136	253	80	132		92	221	131	216
252	124	CTGT	94	221	96	208	106	233		89	208	98	218
253	133	GACA	108	243	110	241	87	[illegible]		90	214	99	219
254	136	GACT	86	188	103	227	159	254		93	228	110	224
255	68	CAAT	99	235	99	214	105	227		94	229	99	226
256	80	CATT	94	217	87	180	348	256	*838.83		255	178	227

Fig. 15(con't)

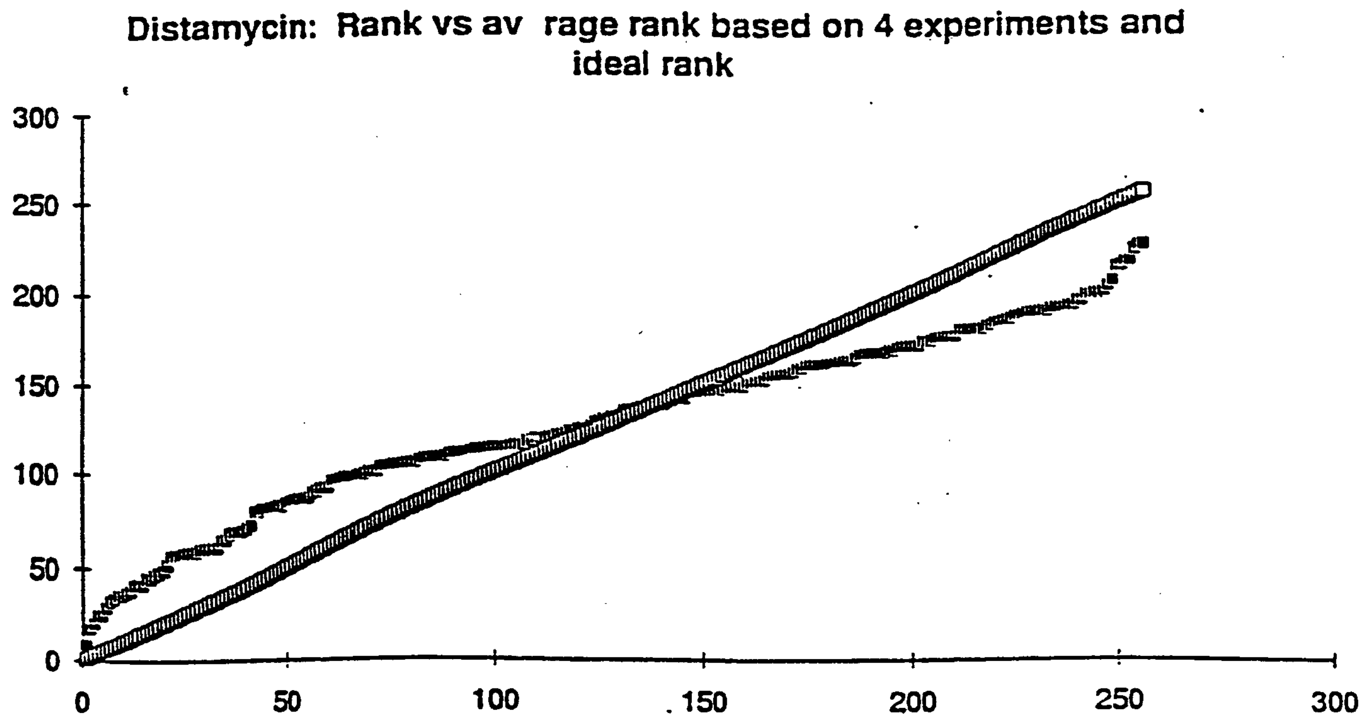

Distamycin: Rank vs av rage rank based on 4 experiments and ideal rank
300
250
200
150
100
50
0
0
50
100
150
200
250
300

Fig. 16

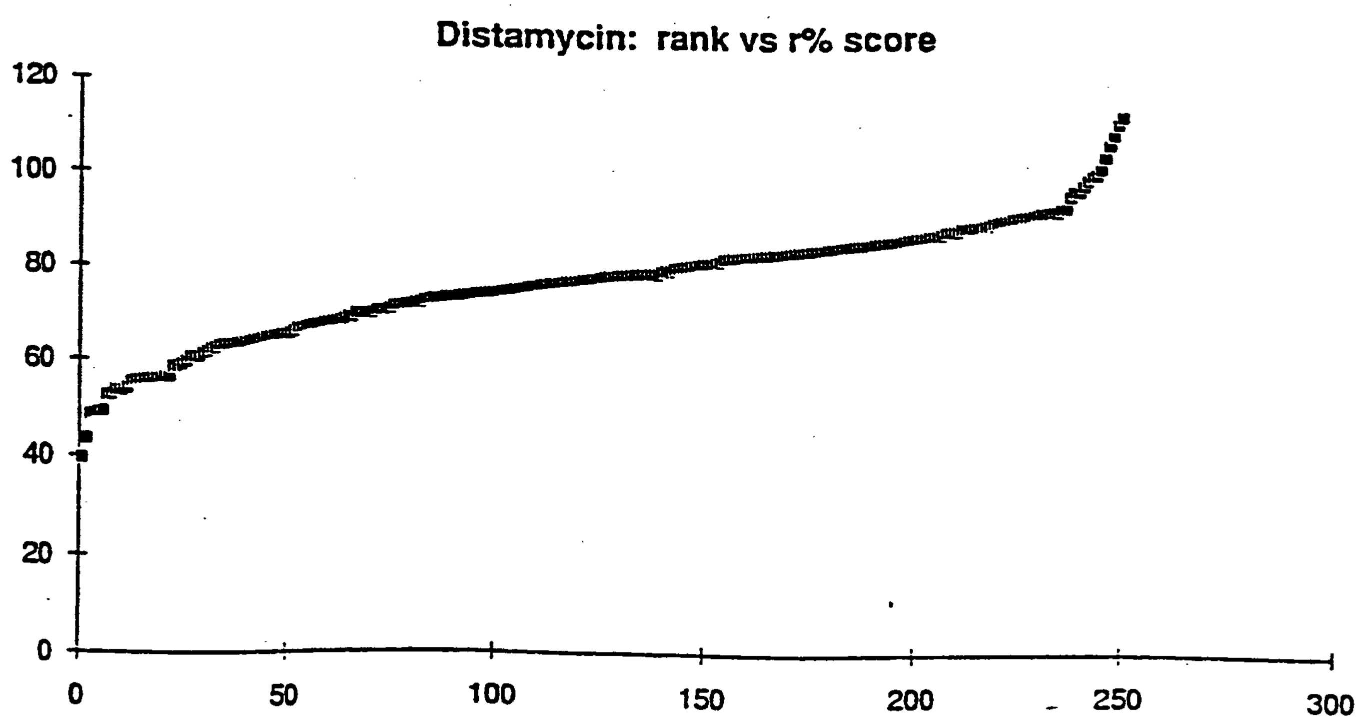

Distamycin: rank vs r% score
120
100
80
60
40
20
0
0
50
100
150
200
250
300

Fig. 17

Actinomycin D Screens

Actinomycin D screens																					
Rank Order	oligo sequence	Screen A %r	rank	Screen B %r	rank	Screen C %r	rank	Screen D %r	rank	Screen E %r	rank	Screen F %r	rank	Screen G %r	rank	Screen H %r	rank	Average % Bound	Average Rank	Rank Order	oligo
1	155 GCGG	60.57	59	46.11	4	37.63	2	44.02	23	42.29	4	38.20	8	34.00	2	29.96	4	41.60	13.25	1	155
2	153 GCGA	39.38	5	58.55	13	48.16	8	53.50	42	55.55	23	45.91	17	34.13	4	23.44	2	44.83	14.25	2	153
3	145 GCAA	50.93	23	62.15	18	52.78	15	54.21	45	40.63	2	53.49	37	34.10	3	34.92	8	47.90	18.88	3	145
4	156 GCGT	60.46	57	67.86	32	N/A	N/A	43.71	22	54.34	20	27.70	1	38.75	5	30.84	6	45.95	20.43	4	156
5	151 GCCG	40.61	6	56.30	9	56.74	25	52.18	38	62.62	46	51.43	31	38.12	6	29.18	3	48.40	20.50	5	151
6	75 CAGG	44.18	13	66.99	30	56.07	24	42.54	20	60.96	43	45.78	15	52.39	30	38.96	12	50.98	23.38	6	75
7	146 GCAC	59.55	49	67.11	31	48.38	9	52.23	39	53.97	18	49.68	25	31.57	1	41.08	16	50.44	23.50	7	148
8	148 GCAT	48.01	20	44.74	3	47.41	7	37.09	13	48.95	10	72.50	113	46.77	17	30.33	5	46.98	23.50	8	148
9	149 GCCA	41.26	8	71.02	57	57.71	28	56.10	52	52.77	13	45.84	16	45.61	14	38.90	11	51.15	24.88	9	149
10	123 CTGG	41.41	9	47.23	5	52.90	16	38.33	15	57.05	27	45.98	18	63.29	95	54.06	51	50.03	29.50	10	123
11	150 GCCG	62.68	67	71.19	58	47.09	6	51.80	36	53.27	15	39.32	9	48.13	21	44.99	25	52.31	29.63	11	150
12	159 GCTG	52.56	28	75.16	89	68.03	67	35.56	11	50.54	12	42.24	12	45.75	15	36.09	10	50.74	30.50	12	159
13	171 GGGG	64.05	79	67.88	33	54.73	20	31.55	5	58.61	32	47.56	20	48.91	26	47.67	30	52.62	30.63	13	171
14	170 GGGC	59.34	47	69.04	47	64.46	51	48.86	28	54.20	19	49.88	28	44.85	12	44.06	22	54.33	31.50	14	170
15	90 CCGC	38.78	4	74.60	81	55.26	22	50.57	31	67.01	61	36.91	6	N/A	N/A	44.71	23	52.55	32.57	15	90
16	147 GCAG	60.36	54	78.98	126	51.43	13	48.35	27	41.47	3	N/A	N/A	42.29	9	17.89	1	48.68	33.29	16	147
17	160 GCTT	65.45	86	60.43	17	44.44	5	43.40	21	59.36	36	60.80	65	49.31	27	43.52	20	53.34	34.63	17	160
18	152 GCCT	66.55	91	58.49	12	N/A	N/A	46.77	25	59.52	38	59.72	61	39.45	7	39.31	15	52.83	35.57	18	152
19	161 GGAA	57.36	40	71.27	60	55.18	21	55.13	47	56.33	24	49.55	24	55.07	38	51.67	39	56.44	36.63	19	161
20	157 GCTA	59.75	51	75.10	87	61.83	39	53.52	43	56.75	25	53.54	38	43.75	11	39.02	13	55.41	38.38	20	157
21	84 CCAT	45.31	16	74.70	83	50.42	10	58.54	56	62.42	45	N/A	N/A	48.20	22	N/A	N/A	56.60	38.67	21	84
22	122 CTGC	43.98	12	84.23	168	25.02	1	33.34	7	59.29	34	52.36	34	54.94	37	44.90	24	49.76	39.63	22	122
23	158 GCTC	57.76	44	77.87	114	60.68	31	55.48	49	56.77	26	53.87	40	46.64	16	46.27	28	56.92	43.50	23	158
24	162 GGAC	55.84	35	64.55	23	61.23	38	50.92	34	66.79	58	62.93	71	59.85	70	54.50	52	59.58	47.38	24	162
25	194 TAAC	44.69	15	68.08	37	37.70	3	60.31	67	57.80	30	73.92	123	56.25	45	56.29	61	56.88	47.63	25	194
26	154 GCGC	56.47	36	95.76	233	66.07	56	47.44	26	28.56	1	35.46	4	43.03	10	42.84	17	51.95	47.88	26	154
27	164 GGAT	60.37	55	77.48	112	51.38	12	55.13	48	63.83	50	52.73	35	55.54	39	49.89	33	58.29	48.00	27	164
28	174 GGTC	72.42	134	59.19	15	62.18	40	53.34	41	66.26	56	54.10	41	54.49	34	50.30	35	59.04	49.50	28	174
29	163 GGAG	59.48	48	72.78	72	65.90	54	60.50	68	65.59	54	62.54	70	56.87	48	42.89	18	60.82	54.00	29	163
30	119 CTCG	51.75	26	51.20	7	67.33	62	37.20	14	79.06	159	57.10	55	59.60	67	53.13	46	57.05	54.50	30	119
31	120 CTCT	60.01	52	63.68	22	53.91	18	27.93	2	110.40	237	44.83	13	47.47	19	58.88	78	58.39	55.13	31	120
32	176 GGTT	71.11	126	70.88	55	71.18	89	33.44	8	67.62	65	56.34	51	48.78	25	45.94	27	58.16	55.75	32	176
33	92 CCGT	41.58	10	31.15	1	66.84	58	63.24	89	73.85	116	68.91	88	61.63	80	50.58	36	57.22	59.75	33	92
34	74 CAGC	59.24	46	75.14	88	61.63	38	49.93	30	69.51	76	54.13	42	63.97	105	55.24	57	61.10	60.25	34	74
35	118 CTCC	61.32	61	39.91	2	160.43	230	49.60	29	44.22	6	57.04	54	58.65	62	52.10	40	65.43	60.50	35	118
36	195 TAAG	60.56	58	68.82	46	67.37	63	N/A	N/A	71.34	92	67.95	82	57.63	52	48.79	32	63.21	60.71	36	195
37	172 GGGT	68.78	106	51.13	6	N/A	N/A	N/A	N/A	78.73	158	62.08	68	45.43	13	39.11	14	57.54	60.83	37	172
38	97 CGAA	40.88	7	108.66	250	62.54	43	34.55	9	45.87	8	N/A	N/A	56.12	43	57.53	69	58.02	61.29	38	97
39	78 CATC	53.97	31	75.77	93	70.36	79	45.96	24	64.06	51	55.29	44	N/A	N/A	63.57	120	61.28	63.14	39	78
40	173 GGTA	70.86	120	72.53	69	54.30	19	50.71	33	71.76	97	38.16	7	72.85	186	51.58	38	60.34	71.13	40	173
41	190 GTTC	65.87	89	62.58	20	56.80	26	70.38	146	49.41	11	72.27	111	63.68	98	58.47	75	62.43	72.00	41	190
42	28 ACGC	68.19	102	70.11	51	65.99	55	38.55	16	67.75	66	87.20	203	53.17	31	54.69	53	63.21	72.13	42	28
43	94 CCTC	77.84	176	78.45	118	69.99	74	53.25	40	55.10	21	68.33	85	50.77	28	52.54	41	63.28	72.88	43	94
44	193 TAAA	62.35	65	66.98	29	62.47	42	81.83	220	48.32	9	72.13	107	41.67	8	63.60	121	62.42	75.13	44	193

Fig. 18(1)

Actinomycin D Screens

45	98 CGAC	43.00	11	76.73	102	N/A	N/A	66.67	122	57.17	28	77.94	155	59.62	68	53.99	48	62.16	76.29	45	98
46	91 CCGG	37.67	3	77.48	111	N/A	N/A	60.54	69	52.81	14	N/A	N/A	79.40	222	52.95	44	60.14	77.17	46	91
47	243 TTAG	51.43	25	62.56	19	105.85	217	54.83	46	68.07	68	75.78	134	60.31	71	53.08	45	66.49	78.13	47	243
48	166 GGCC	63.70	76	83.98	164	55.83	23	73.29	176	53.29	16	47.93	22	60.94	74	61.57	101	62.57	81.50	48	166
49	244 TTAT	67.43	97	54.61	8	76.26	128	60.11	64	73.07	109	79.43	165	58.05	58	48.32	31	64.66	82.50	49	244
50	196 TAAT	78.47	179	66.80	28	51.75	14	N/A	N/A	69.98	79	82.49	185	56.19	44	55.14	55	65.83	83.43	50	196
51	82 CCAC	73.84	144	83.47	159	86.64	187	55.84	51	43.07	5	61.83	67	54.65	36	43.50	19	62.85	83.50	51	82
52	138 GAGC	65.53	88	84.11	165	71.29	91	60.24	66	58.70	33	41.87	11	69.61	152	57.12	67	63.56	84.13	52	138
53	71 CACG	67.02	94	69.66	49	57.96	29	62.29	81	71.29	88	56.54	52	57.97	55	83.33	228	65.76	84.50	53	71
54	202 TAGC	81.74	206	83.44	158	74.12	110	30.93	4	57.63	29	51.92	33	53.78	32	62.78	111	62.04	85.38	54	202
55	250 TTGC	75.37	156	87.05	186	72.08	97	29.06	3	71.76	96	64.95	73	57.02	49	46.82	29	63.01	86.13	55	250
56	27 ACGG	66.61	92	80.03	133	71.62	93	67.29	126	45.40	7	81.44	180	57.66	53	34.56	7	63.08	86.38	56	27
57	57 ATGA	77.49	168	90.13	210	62.87	45	63.06	86	73.29	111	51.51	32	47.38	18	43.87	21	63.70	86.38	57	57
58	132 GAAT	73.50	141	86.93	184	62.25	41	56.35	53	77.91	153	33.80	3	59.09	64	55.79	59	63.20	87.25	58	132
59	251 TTGG	69.22	111	59.03	14	N/A	N/A	61.91	77	75.50	128	79.60	166	62.10	84	52.61	42	65.71	88.86	59	251
60	186 GTGC	50.43	22	77.20	105	N/A	N/A	77.04	198	N/A	N/A	55.38	45	61.30	77	60.15	88	63.58	89.17	60	186
61	180 GTAT	69.01	108	77.53	113	N/A	N/A	62.19	79	70.37	81	51.35	30	61.06	75	66.70	143	65.46	89.86	61	180
62	30 ACTC	63.85	78	71.43	61	76.78	133	73.84	180	72.55	104	55.77	47	61.40	78	53.99	49	66.20	91.25	62	30
63	4 AAAT	73.87	146	68.75	44	63.52	46	N/A	N/A	68.90	71	80.07	168	59.68	69	63.55	119	68.33	94.71	63	4
64	140 GAGT	65.50	87	68.60	43	81.50	168	68.10	131	55.38	22	72.01	106	69.75	154	56.56	62	67.17	96.63	64	140
65	31 ACTG	77.20	167	73.83	77	117.29	221	54.07	44	71.45	93	58.57	58	56.10	42	59.14	79	70.95	97.63	65	31
66	178 GTAG	61.36	62	71.74	63	93.90	205	64.94	103	60.33	41	69.14	89	66.03	126	61.09	98	68.57	98.38	66	178
67	175 GGTG	68.31	104	86.21	181	110.54	220	68.74	137	63.73	48	55.88	48	48.69	24	45.23	26	68.42	98.50	67	175
68	7 AACG	68.40	105	83.42	156	72.35	99	69.29	142	72.53	103	53.85	39	61.67	81	56.74	64	67.28	98.63	68	7
69	79 CATG	57.47	41	95.73	231	N/A	N/A	62.70	82	59.31	35	N/A	N/A	56.67	46	68.61	164	66.75	99.83	69	79
70	255 TTTG	71.02	122	102.27	247	64.12	50	59.40	61	59.82	39	72.54	114	63.90	102	57.10	66	68.77	100.13	70	255
71	29 ACTA	65.30	85	71.48	62	85.39	185	63.66	92	82.22	179	51.02	29	61.85	83	60.07	87	67.62	100.25	71	29
72	256 TTTT	73.85	145	88.88	200	72.92	104	60.98	71	60.55	42	76.19	138	56.85	47	55.49	58	68.21	100.63	72	256
73	77 CATA	45.90	17	76.72	101	63.84	47	62.16	78	67.89	67	N/A	N/A	74.86	200	76.18	199	66.79	101.29	73	77
74	83 CCAG	31.15	1	58.14	11	N/A	N/A	63.10	87	81.37	176	67.36	81	71.18	174	71.90	179	63.46	101.29	74	83
75	247 TTCG	69.06	109	60.09	16	168.33	231	68.62	136	74.92	122	59.22	60	57.85	54	60.23	90	77.04	102.25	75	247
76	76 CAGT	52.35	27	68.33	39	69.51	73	84.51	223	62.64	47	73.72	122	70.33	165	64.84	129	68.28	103.13	76	76
77	93 CCTA	51.13	24	89.50	207	70.81	85	65.38	107	N/A	N/A	47.85	21	74.06	194	59.98	85	65.53	103.29	77	93
78	18 ACAC	91.71	246	72.56	70	N/A	N/A	61.60	74	63.79	49	77.56	152	60.48	73	57.57	70	69.32	104.86	78	18
79	96 CCTT	67.50	98	87.74	192	80.15	160	35.55	10	75.52	129	N/A	N/A	55.86	41	N/A	N/A	67.05	105.00	79	96
80	198 TACC	79.63	189	83.31	154	67.73	65	58.29	54	53.62	17	75.92	135	64.41	110	63.37	117	68.28	105.13	80	198
81	188 GTGT	66.82	93	65.68	27	N/A	N/A	60.60	70	83.11	186	76.88	144	67.53	137	59.33	80	68.56	105.29	81	188
82	131 GAAG	71.56	129	56.81	10	77.86	146	162.35	244	69.45	75	67.31	80	64.55	113	54.04	50	77.99	105.88	82	131
83	58 ATGC	79.53	187	82.93	151	103.10	216	63.78	94	61.71	44	46.36	19	51.19	29	62.86	113	68.93	106.63	83	58
84	10 AAGC	85.40	222	89.00	201	80.61	163	61.87	75	N/A	N/A	57.84	57	47.53	20	36.08	9	65.48	106.71	84	10
85	102 CGCC	63.63	75	78.60	120	71.74	94	69.04	140	85.17	199	63.39	72	57.14	50	N/A	N/A	69.82	107.14	85	102
86	179 GTAG	69.21	110	80.15	134	70.28	77	88.42	233	72.97	106	62.48	69	63.71	99	50.09	34	69.66	107.75	86	179
87	126 CTTC	70.58	116	75.24	90	73.83	108	61.26	72	72.59	105	53.06	36	77.14	214	63.83	122	68.44	107.88	87	126
88	253 TTTA	78.85	182	79.98	132	71.25	90	63.10	88	67.09	63	73.29	118	54.50	35	67.89	156	69.49	108.00	88	253
89	19 ACAG	77.59	173	74.85	86	78.05	149	62.96	85	70.40	82	77.05	146	58.01	56	60.51	92	69.93	108.63	89	19
90	66 CAAC	66.52	90	75.24	91	90.63	196	60.15	65	68.83	70	68.56	87	73.52	189	59.47	82	70.36	108.75	90	66
91	25 ACGA	47.26	19	71.84	64	77.06	137	62.81	84	84.75	196	N/A	N/A	58.05	57	77.52	209	68.47	109.43	91	25

Fig. 18(2)

Actinomycin D Screens

92	99 CGAG	62.90	70	79.03	127	70.55	80	79.84	212	73.07	108	80.31	169	55.55	40	57.60	71	69.86	109.63	92	99
93	106 CGGC	69.82	112	68.07	36	96.25	210	63.80	95	70.03	80	77.45	150	58.37	59	66.08	139	71.23	110.13	93	106
94	133 GACA	70.88	121	75.86	95	66.91	59	71.95	165	65.72	55	N/A	N/A	61.56	79	76.62	203	69.93	111.00	94	133
95	221 TCTA	54.90	32	64.80	25	128.91	226	66.73	123	70.82	85	66.86	78	66.22	129	75.29	194	74.32	111.50	95	221
96	201 TAGA	73.16	140	70.43	53	75.52	119	69.57	144	69.31	73	88.58	205	65.38	119	52.93	43	70.61	112.00	96	201
97	107 CGGG	78.98	183	64.60	24	74.68	114	51.58	35	86.06	204	79.33	163	62.89	91	60.78	94	69.86	113.50	97	107
98	139 GAGG	68.24	103	76.19	97	83.24	178	66.31	118	58.16	31	N/A	N/A	70.92	169	61.10	99	69.17	113.57	98	139
99	169 GGGA	73.64	142	96.71	237	93.34	204	39.69	17	77.89	152	60.45	64	53.90	33	57.22	68	69.10	114.63	99	169
100	62 ATAT	75.03	154	68.77	45	66.77	57	62.26	80	68.39	69	68.12	83	86.84	243	74.43	187	71.33	114.75	100	62
101	129 GAAA	77.60	174	74.43	80	70.19	76	58.73	57	90.36	218	59.82	62	72.41	185	58.50	76	70.26	116.00	101	129
102	224 TCTT	61.96	63	74.26	79	76.77	132	71.36	157	67.08	62	76.59	142	63.23	94	76.19	200	70.93	116.13	102	224
103	87 CCCG	57.14	39	72.04	66	70.63	81	59.20	60	75.84	133	108.76	223	75.22	202	64.94	130	72.97	116.75	103	87
104	144 GATT	82.90	214	85.93	179	61.35	37	65.23	106	71.51	95	48.53	23	64.44	111	70.04	169	68.74	116.75	104	144
105	81 CCAA	60.24	53	81.34	141	66.98	60	73.43	177	83.02	185	32.30	2	66.46	130	74.45	188	67.28	117.00	105	81
106	241 TTAA	72.94	138	70.48	54	76.35	129	71.63	162	69.62	77	69.68	92	72.05	181	62.28	108	70.63	117.63	106	241
107	100 CGAT	46.56	18	77.40	109	86.01	186	83.70	93	77.51	149	70.74	99	59.23	65	80.63	223	70.22	117.75	107	100
108	121 CTGA	44.48	14	95.99	235	N/A	N/A	59.19	59	87.65	211	N/A	N/A	62.57	86	61.75	104	68.61	118.17	108	121
109	64 ATTT	63.10	71	73.69	76	71.00	87	65.94	112	69.14	72	82.91	186	67.59	139	76.66	204	71.25	118.38	109	64
110	17 ACAA	89.62	238	78.08	116	74.84	117	63.95	96	70.74	84	60.39	63	63.63	96	66.99	145	71.03	119.38	110	17
111	189 GTTA	59.71	50	78.39	117	79.82	157	65.19	105	93.49	224	50.60	28	69.99	156	63.40	118	70.07	119.38	111	189
112	73 CAGA	64.95	83	83.20	153	67.48	64	67.89	130	75.69	130	N/A	N/A	64.18	107	71.02	173	70.63	120.00	112	73
113	70 CACC	77.50	169	70.23	52	93.28	203	N/A	N/A	66.61	57	97.69	215	58.76	61	59.99	86	74.87	120.43	113	70
114	218 TCGC	97.46	252	77.27	107	60.99	34	78.02	205	N/A	N/A	68.42	86	58.94	63	61.07	97	71.74	120.57	114	218
115	124 CTGT	70.70	117	84.59	172	71.31	92	64.69	101	76.75	141	66.15	77	67.51	136	65.74	134	70.93	121.25	115	124
116	101 CGCA	64.43	81	77.35	108	70.35	78	84.56	224	80.07	165	76.11	137	57.21	51	64.98	131	71.88	121.88	116	101
117	59 ATGG	79.34	186	138.30	254	57.31	27	59.53	62	94.28	226	36.05	5	65.84	125	60.87	95	73.94	122.50	117	59
118	184 GTCT	55.42	33	81.97	144	80.96	165	105.72	241	N/A	N/A	44.89	14	69.67	153	62.33	109	71.57	122.71	118	184
119	167 GGCG	71.79	130	72.81	73	81.64	169	84.48	222	71.87	98	72.24	109	64.25	108	59.66	83	72.34	124.00	119	167
120	191 GTTG	61.96	64	82.68	149	83.67	180	84.99	226	78.55	157	40.73	10	70.21	162	53.17	47	69.49	124.38	120	191
121	222 TCTC	56.59	37	73.49	75	N/A	N/A	88.12	232	74.72	121	69.89	95	67.43	135	71.74	177	71.71	124.57	121	222
122	28 ACGT	62.71	68	68.36	40	71.00	88	63.29	90	110.06	236	71.53	104	80.50	225	67.45	150	74.36	125.13	122	28
123	249 TTGA	56.92	38	71.87	65	82.61	175	N/A	N/A	87.81	212	77.68	153	65.36	118	63.20	116	72.21	125.29	123	249
124	177 GTAA	74.68	152	76.05	96	82.21	171	67.64	128	87.60	209	69.79	93	63.18	93	57.09	65	72.28	125.88	124	177
125	80 CATT	53.28	30	85.96	180	76.72	130	65.92	111	75.23	125	72.55	115	70.13	160	69.02	166	71.10	127.13	125	80
126	187 GTGG	49.60	21	98.27	242	108.71	219	74.66	184	73.09	110	54.24	43	67.14	131	58.25	73	73.00	127.88	126	187
127	245 TTCA	57.49	42	84.27	170	79.74	156	33.20	6	82.51	182	70.50	97	68.34	142	84.81	231	70.11	128.25	127	245
128	82 ATTC	77.57	172	82.26	146	70.69	83	59.98	63	77.00	144	50.17	27	71.98	178	80.17	221	71.23	129.25	128	82
129	165 GGCA	60.85	60	85.87	177	77.38	141	50.70	32	95.68	230	65.20	75	78.36	218	61.68	102	71.96	129.38	129	165
130	203 TAGG	83.46	218	63.09	21	75.82	121	71.34	155	71.94	99	71.05	101	64.32	109	78.89	216	72.49	130.00	130	203
131	199 TACG	80.64	197	71.25	59	68.65	70	66.59	120	103.91	234	59.12	59	107.68	248	55.14	54	76.62	130.13	131	199
132	50 ATAC	79.80	191	84.11	166	66.98	61	79.99	215	80.63	170	55.61	46	62.89	90	61.75	103	71.47	130.25	132	50
133	246 TTCC	73.71	143	78.62	121	82.12	170	79.89	213	77.01	145	71.50	103	48.57	23	64.70	128	72.01	130.75	133	246
134	130 GAAC	72.36	132	83.69	160	124.36	225	71.56	161	67.35	64	73.07	116	64.67	115	58.40	74	76.93	130.88	134	130
135	33 AGAA	70.76	118	70.89	56	77.15	138	42.19	19	81.86	177	91.67	209	84.34	233	61.18	100	72.50	131.25	135	33
136	114 CTAC	70.20	114	77.21	106	N/A	N/A	71.81	164	72.23	101	71.39	102	73.41	188	66.85	144	71.87	131.29	136	114
137	32 ACTT	71.10	125	76.57	99	75.96	123	72.19	167	74.96	123	65.31	76	72.31	183	67.96	157	72.05	131.63	137	32
138	137 GAGA	67.88	101	90.21	214	68.49	69	27.69	1	59.49	37	101.67	218	70.28	164	116.99	249	75.34	131.63	138	137

Fig. 18(3)

Actinomycin D Screens

139	110 CGTC	75.37	158	90.14	211	60.78	32	64.62	99	76.01	135	72.24	110	70.41	167	66.33	142	71.99	131.75	139	110
140	205 TATA	76.38	165	78.80	125	64.00	48	68.41	133	78.22	155	81.07	175	N/A	N/A	65.13	132	73.14	133.29	140	205
141	219 TCGG	75.75	162	78.79	124	77.75	144	85.57	228	80.79	172	61.80	66	64.05	106	58.22	72	72.84	134.25	141	219
142	54 ATCC	87.49	233	85.52	175	N/A	N/A	55.49	50	84.75	197	69.39	90	62.58	88	62.26	107	72.50	134.29	142	54
143	3 AAAG	74.56	151	139.01	255	71.76	95	72.23	168	69.81	78	76.46	141	65.79	124	56.63	63	78.28	134.38	143	3
144	252 TTGT	74.55	150	90.30	215	75.85	122	65.62	109	N/A	N/A	75.12	129	59.40	66	67.54	152	72.63	134.71	144	252
145	48 AGTC	72.75	136	81.56	143	80.26	161	65.45	108	71.20	87	87.74	204	65.73	123	64.30	125	73.63	135.88	145	48
146	168 GGCT	74.25	147	81.52	142	50.55	11	73.26	175	73.86	117	67.19	79	80.70	226	75.37	195	72.09	136.50	146	168
147	208 TATT	88.36	236	73.98	78	70.11	75	65.10	104	73.70	115	81.39	179	69.39	151	67.87	155	73.74	136.63	147	208
148	185 GTGA	59.16	45	94.17	228	83.61	179	51.86	37	114.85	238	56.26	50	68.56	147	70.16	170	74.83	136.75	148	185
149	95 CGTG	60.41	56	72.75	71	79.13	154	66.06	115	N/A	N/A	86.62	199	86.12	239	64.49	127	73.66	137.29	149	95
150	89 CCGA	33.81	2	83.89	163	N/A	N/A	77.77	204	64.97	52	71.83	105	74.05	193	95.06	244	71.62	137.57	150	89
151	242 TTAC	71.05	123	68.46	42	76.73	131	74.29	182	77.10	146	78.77	158	67.56	138	73.88	186	73.48	138.25	151	242
152	49 ATAA	90.67	243	75.72	92	72.47	100	78.06	206	78.40	156	N/A	N/A	64.56	114	56.07	60	73.70	138.71	152	49
153	11 AAGG	77.83	175	67.92	35	74.69	115	72.74	172	87.62	210	80.45	170	61.13	76	68.56	163	73.87	139.50	153	11
154	9 AAGA	79.67	190	87.30	189	70.90	88	71.17	152	76.63	139	98.05	216	63.03	92	55.16	56	75.24	140.00	154	9
155	63 ATTG	67.08	95	93.18	223	72.20	98	64.04	97	74.11	118	83.70	187	68.98	148	68.14	158	73.93	140.50	155	63
156	105 CGGA	82.96	215	72.33	68	72.83	103	74.96	186	88.16	214	N/A	N/A	58.40	60	66.05	138	73.67	140.57	156	105
157	192 GTTT	63.61	74	98.11	241	139.09	228	63.49	91	125.14	240	56.74	53	62.74	89	62.54	110	83.93	140.75	157	192
158	207 TATG	79.23	185	90.15	212	59.59	30	74.94	185	74.35	119	74.77	126	68.54	146	64.20	124	73.22	140.88	158	207
159	51 ATAG	93.62	249	87.02	185	65.34	52	68.45	134	75.90	134	102.67	220	65.02	117	50.60	37	76.08	141.00	159	51
160	135 GACG	75.37	157	78.50	119	82.57	174	61.50	73	78.79	142	86.71	201	69.99	157	61.89	105	74.17	141.00	160	135
161	209 TCAA	80.79	198	81.32	140	60.93	33	76.22	193	70.48	83	75.34	131	69.32	150	76.40	201	73.85	141.13	161	209
162	20 ACAT	90.38	241	88.41	196	69.38	72	70.27	145	71.98	100	74.35	125	66.20	128	64.05	123	74.38	141.25	162	20
163	230 TGCC	63.40	73	73.36	74	84.01	182	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	87.55	236	77.08	141.25	163	230
164	22 ACCC	69.83	113	84.20	167	360.73	232	40.14	18	67.00	60	81.62	183	70.05	158	76.84	205	106.30	142.00	164	22
165	104 CGCT	82.57	212	74.62	82	94.87	207	72.49	171	78.21	154	73.70	121	62.50	85	63.06	114	75.25	143.25	165	104
166	197 TACA	80.55	195	88.11	195	64.01	49	84.73	225	65.51	53	76.00	136	65.44	121	71.63	175	74.50	143.63	166	197
167	6 AACC	80.18	192	93.97	225	N/A	N/A	71.52	160	72.97	107	N/A	N/A	63.67	97	59.42	81	73.62	143.67	167	6
168	183 GTCG	53.05	29	79.84	131	95.24	208	69.04	139	90.32	217	70.64	98	70.07	159	70.96	172	74.89	144.13	168	183
169	65 CAAA	62.52	66	78.65	123	82.95	176	71.47	159	73.47	112	77.24	147	71.90	177	75.43	196	74.20	144.50	169	65
170	53 ATCA	77.99	177	89.12	203	73.53	106	62.74	83	76.35	136	72.15	108	65.43	120	84.40	230	75.21	145.38	170	53
171	67 CAAG	72.17	131	107.82	249	76.00	125	68.08	114	71.31	90	N/A	N/A	69.88	155	67.72	154	75.85	145.43	171	67
172	206 TATC	77.57	171	89.46	206	62.84	44	75.93	189	60.27	40	78.34	139	78.75	210	69.56	167	73.59	145.75	172	206
173	36 AGAT	80.96	201	75.78	94	53.13	17	70.42	147	76.36	137	83.92	188	74.06	195	74.52	189	73.64	146.00	173	36
174	103 CGCG	125.02	255	72.32	67	80.36	162	67.56	127	97.53	231	N/A	N/A	63.89	101	59.86	84	80.93	146.71	174	103
175	128 CTTT	72.98	139	87.83	193	72.04	96	58.86	58	89.18	216	72.37	112	83.53	231	65.66	133	75.31	147.25	175	128
176	200 TACT	87.43	232	65.63	26	67.96	66	79.20	209	80.78	171	80.56	172	74.16	196	61.91	106	74.70	147.25	176	200
177	220 TCGT	87.10	230	79.06	128	83.88	181	66.97	125	72.39	102	79.15	162	64.48	112	N/A	N/A	76.15	148.57	177	220
178	211 TCAG	81.49	204	90.60	217	79.92	158	66.02	113	75.78	132	74.83	128	67.31	134	62.85	112	74.85	149.75	178	211
179	223 TCTG	72.42	135	95.29	230	91.12	198	74.14	181	69.37	74	75.15	130	63.92	103	67.58	153	76.13	150.50	179	223
180	16 AATT	84.54	220	69.46	48	78.00	148	66.60	121	77.27	147	74.02	124	75.56	204	77.01	207	75.31	152.38	180	16
181	111 CGTG	75.03	155	82.01	145	68.12	68	68.50	135	79.35	162	73.27	117	73.68	191	99.19	246	77.39	152.38	181	111
182	125 CTTA	70.81	119	81.09	139	73.96	109	67.71	129	N/A	N/A	N/A	N/A	71.71	176	99.86	247	77.52	153.17	182	125
183	60 ATGT	80.44	194	84.45	171	44.43	4	70.75	150	82.79	183	75.41	132	90.44	247	67.00	146	74.46	153.38	183	60
184	210 TCAC	63.73	77	76.53	98	79.92	159	36.31	12	104.55	235	92.68	212	78.24	217	78.90	217	76.36	153.38	184	210
185	141 GATA	95.02	250	74.84	85	91.21	199	N/A	N/A	74.53	120	73.29	119	76.49	208	60.61	93	78.00	153.43	185	141

Fig. 18(4)

Actinomycin D Screens

186	34 AGAC	78.50	180	79.13	129	101.67	215	71.63	163	71.47	94	79.05	161	67.18	132	68.46	160	77.14	154.25	186	34
187	204 TAGT	91.18	245	84.25	169	92.03	201	72.26	169	66.86	59	69.40	91	68.99	149	68.61	165	76.70	156.00	187	204
188	181 GTCA	114.04	254	83.39	155	100.90	214	61.90	76	84.12	190	74.78	127	62.57	87	67.42	149	81.14	156.50	188	181
189	142 GATC	72.41	133	89.04	202	87.57	192	70.76	151	75.33	126	86.29	197	70.13	161	60.39	91	76.49	156.63	189	142
190	116 CTAT	80.41	193	96.23	236	77.22	139	N/A	N/A	70.87	86	76.94	145	71.01	172	64.33	126	76.71	156.71	190	116
191	42 AGGC	72.91	137	81.02	137	N/A	N/A	79.09	208	87.53	208	57.36	56	85.93	238	63.20	115	75.29	157.00	191	42
192	1 AAAA	87.21	231	78.63	122	77.71	143	68.37	132	87.37	205	N/A	N/A	66.09	127	66.30	141	75.95	157.29	192	1
193	134 GACC	77.53	170	67.89	34	148.56	229	69.47	143	83.83	189	77.31	149	70.25	163	72.45	182	83.41	157.38	193	134
194	254 TTTC	80.58	196	89.83	209	N/A	N/A	66.43	119	76.70	140	80.53	171	63.79	100	70.39	171	75.46	158.00	194	254
195	117 CTCA	86.48	228	83.86	162	76.84	134	64.64	100	98.87	232	81.15	176	68.49	145	61.01	96	77.67	159.13	195	117
196	136 GACT	80.80	199	125.62	253	75.66	120	72.33	170	80.16	166	70.97	100	73.65	190	58.85	77	79.75	159.38	196	136
197	115 CTAG	75.57	161	103.17	248	77.36	140	69.02	138	N/A	N/A	N/A	N/A	67.27	133	66.00	137	76.40	159.50	197	115
198	72 CACT	75.54	159	84.94	174	N/A	N/A	75.76	188	75.12	124	N/A	N/A	61.70	82	85.97	232	76.50	159.83	198	72
199	15 AATG	90.31	240	91.51	219	70.79	84	71.42	158	76.96	143	78.95	160	68.18	141	65.78	135	76.74	160.00	199	15
200	143 GATG	82.18	209	77.08	104	82.35	172	75.16	187	N/A	N/A	56.13	49	70.94	170	83.55	229	75.34	160.00	200	143
201	61 ATTA	86.48	227	87.73	191	75.97	124	71.18	153	73.55	113	N/A	N/A	60.48	72	91.80	241	78.17	160.14	201	61
202	35 AGAG	80.89	200	68.45	41	87.40	191	64.52	98	80.52	168	81.53	182	75.82	206	78.70	214	77.23	162.50	202	35
203	85 CCCA	88.24	235	85.91	178	81.43	187	58.51	55	73.63	114	N/A	N/A	72.00	180	78.82	215	76.93	163.43	203	85
204	68 CAAT	70.31	115	90.37	216	80.88	164	71.31	154	77.69	150	81.51	181	71.16	173	68.53	161	76.47	164.25	204	68
205	14 AATC	90.09	239	89.40	205	68.88	71	70.66	148	81.08	174	78.27	157	72.36	184	66.14	140	77.11	164.75	205	14
206	248 TTCT	67.84	100	68.10	38	90.96	197	N/A	N/A	84.50	192	84.60	190	109.00	249	74.60	190	82.80	165.14	206	248
207	182 GTCC	76.24	164	69.74	50	132.12	227	84.83	102	84.98	198	88.52	198	75.68	205	75.46	198	83.20	167.75	207	182
208	13 AATA	93.48	248	82.69	150	84.97	184	66.82	124	84.59	193	N/A	N/A	63.92	104	72.93	184	78.49	169.57	208	13
209	86 CCCC	65.16	84	93.13	222	117.51	222	77.01	197	80.61	169	64.99	74	73.22	187	76.55	202	81.02	169.63	209	86
210	55 ATCG	88.83	237	82.62	148	121.85	224	70.70	149	80.06	164	N/A	N/A	65.49	122	67.16	148	82.38	170.29	210	55
211	109 CGTA	74.47	148	222.74	256	65.82	53	76.48	194	92.66	221	N/A	N/A	68.45	143	71.90	178	96.08	170.43	211	109
212	227 TGAG	62.76	69	93.96	224	73.79	107	77.12	200	86.01	203	85.01	193	73.72	192	71.94	181	78.04	171.13	212	227
213	127 CTTG	67.24	96	95.73	232	77.04	136	76.63	195	80.43	167	N/A	N/A	77.03	213	68.53	162	77.52	171.57	213	127
214	56 ATCT	79.60	188	98.81	243	97.66	212	95.73	238	75.40	127	78.35	140	67.91	140	60.20	89	81.46	172.13	214	56
215	8 AACT	63.39	72	89.56	208	78.72	152	133.37	243	N/A	N/A	82.01	184	71.98	179	71.48	174	84.36	173.14	215	8
216	39 AGCG	55.62	34	81.03	138	90.52	195	N/A	N/A	94.55	227	98.66	217	78.60	219	73.52	185	81.78	173.57	216	39
217	217 TCGA	74.55	149	87.65	190	70.63	82	80.91	218	87.39	206	76.72	143	74.91	201	78.18	210	78.87	174.88	217	217
218	113 CTAA	81.74	207	82.35	147	74.43	113	73.65	179	79.49	163	116.48	225	68.47	144	81.07	224	82.21	175.25	218	113
219	237 TGTA	78.22	178	74.76	84	120.76	223	80.70	217	71.33	91	79.83	167	80.22	224	80.00	220	83.23	175.50	219	237
220	225 TGAA	81.19	202	83.42	157	84.02	183	85.37	227	77.75	151	69.80	94	76.65	209	72.75	183	78.87	175.75	220	225
221	69 CACA	78.67	181	91.38	218	74.72	116	69.10	141	82.23	180	85.55	194	75.46	203	N/A	N/A	79.59	176.14	221	69
222	112 CGTT	76.02	163	92.06	220	78.20	150	77.13	201	85.76	201	69.94	96	77.00	212	N/A	N/A	79.44	177.57	222	112
223	88 CCCT	64.56	82	83.70	161	72.52	102	89.96	234	82.17	178	92.41	211	132.23	251	76.87	206	86.80	178.13	223	88
224	23 ACCG	92.45	247	79.82	130	83.22	177	72.11	166	79.16	160	75.57	133	72.05	182	86.09	233	80.06	178.50	224	23
225	2 AAAC	86.91	229	86.72	183	77.79	145	76.12	192	85.50	200	81.04	174	70.95	171	65.85	136	78.86	178.75	225	2
226	212 TCAT	82.25	210	100.54	244	74.42	112	81.54	219	79.31	161	85.85	195	64.89	116	71.69	176	80.06	179.13	226	212
227	5 AACA	82.03	208	102.03	246	76.87	135	71.35	156	71.29	89	95.87	214	N/A	N/A	77.15	208	82.37	179.43	227	5
228	47 AGTG	68.89	107	83.05	152	89.02	194	78.89	207	82.81	184	81.22	177	83.88	232	75.15	192	80.36	180.63	228	47
229	214 TCCC	88.19	234	77.05	103	78.22	151	76.96	196	75.69	131	N/A	N/A	89.31	246	78.25	212	80.52	181.86	229	214
230	215 TCCG	90.57	242	80.30	135	82.42	173	73.62	178	76.56	138	89.79	207	80.86	227	68.31	159	80.30	182.38	230	215
231	38 AGCC	86.33	226	77.43	110	87.33	189	80.43	216	83.60	188	78.21	156	77.19	215	69.96	168	80.06	183.50	231	38
232	234 TGGC	64.41	80	88.50	198	N/A	N/A	72.86	173	82.32	181	84.96	192	86.57	241	80.18	222	79.97	183.86	232	234

Fig. 18(5)

Actinomycin D Screens

233	45 AGTA	71.40	128	77.89	115	81.38	166	77.24	202	88.91	215	104.60	222	84.62	234	78.19	211	83.03	186.63	233	45
234	228 TGAT	85.64	223	87.88	194	76.05	126	79.93	214	N/A	N/A	78.86	159	70.36	166	91.45	239	81.45	188.71	234	228
235	213 TCCA	91.13	244	101.29	245	61.15	35	79.36	210	N/A	N/A	85.98	196	74.48	199	75.26	193	81.24	188.86	235	213
236	108 CGGT	83.16	217	90.19	213	73.16	105	104.86	240	93.95	225	79.38	164	70.58	168	75.10	191	83.80	190.38	236	108
237	229 TGCA	71.23	127	87.23	187	79.15	155	87.74	231	87.87	213	77.48	151	86.70	242	79.41	218	82.10	190.50	237	22
238	97 AGCA	83.10	216	85.57	176	87.39	190	68.12	116	90.83	220	N/A	N/A	74.37	197	79.91	219	81.04	190.57	238	37
239	239 TGTG	76.41	166	94.15	227	N/A	N/A	77.07	199	77.32	148	110.58	224	84.72	235	67.09	147	83.91	192.29	239	239
240	231 TGCG	74.69	153	86.37	182	87.30	188	91.97	237	80.94	173	80.57	173	78.96	221	78.64	213	82.43	192.50	240	231
241	226 TGAC	84.64	221	89.18	204	106.84	218	76.03	191	94.57	228	73.50	120	76.82	211	67.50	151	83.63	193.00	241	226
242	236 TGGT	79.11	184	78.66	100	97.31	211	N/A	N/A	81.30	175	102.37	219	82.29	229	87.08	235	86.59	193.29	242	236
243	232 TGCT	57.69	43	95.24	229	91.54	200	82.10	221	84.29	191	91.86	210	83.35	230	83.14	227	83.65	193.88	243	232
244	24 ACCT	96.57	251	84.93	173	76.14	127	73.03	174	90.46	219	84.26	189	74.46	198	87.02	234	83.36	195.63	244	24
245	41 AGGA	81.23	203	93.99	226	77.53	142	91.66	236	93.02	223	68.22	84	113.69	250	90.63	238	88.75	200.25	245	41
246	44 AGGT	83.59	219	80.67	136	94.43	206	65.83	110	95.29	229	104.27	221	86.47	240	92.25	242	87.85	200.38	246	44
247	43 AGGG	86.24	225	97.24	239	N/A	N/A	66.15	117	87.41	207	77.87	154	79.81	223	91.72	240	83.78	200.71	247	43
248	21 ACCA	135.86	256	97.64	240	74.90	118	76.00	190	84.70	195	86.68	200	80.99	228	71.92	180	88.59	200.88	248	21
249	233 TGGA	71.07	124	110.33	252	92.16	202	79.48	211	N/A	N/A	77.27	148	87.17	244	82.74	226	85.75	201.00	249	233
250	40 AGCT	67.69	99	87.27	188	95.79	209	86.79	229	102.52	233	93.53	213	89.04	245	75.44	197	87.26	201.63	250	40
251	12 AAGT	81.66	205	92.86	221	74.22	111	107.95	242	N/A	N/A	89.87	208	71.18	175	118.83	250	90.94	201.71	251	12
252	48 AGTT	82.33	211	96.83	238	87.79	193	74.41	183	83.59	187	81.39	178	78.87	220	81.71	225	83.36	204.38	252	48
253	235 TGGG	75.55	160	88.44	197	98.72	213	96.03	239	85.88	202	84.86	191	85.53	237	88.22	237	87.90	209.50	253	235
254	238 TGTC	85.93	224	88.81	199	78.81	153	77.37	203	118.62	239	N/A	N/A	77.66	216	103.38	248	90.08	211.71	254	238
255	216 TCCT	100.46	253	95.84	234	72.52	101	91.36	235	92.72	222	88.88	206	76.37	207	94.84	243	89.13	212.63	255	216
256	240 TGTT	82.60	213	110.20	251	77.91	147	86.95	230	84.66	194	87.10	202	85.39	236	95.58	245	88.80	214.75	256	240

Fig. 18(6)

Actinomycin D Screens

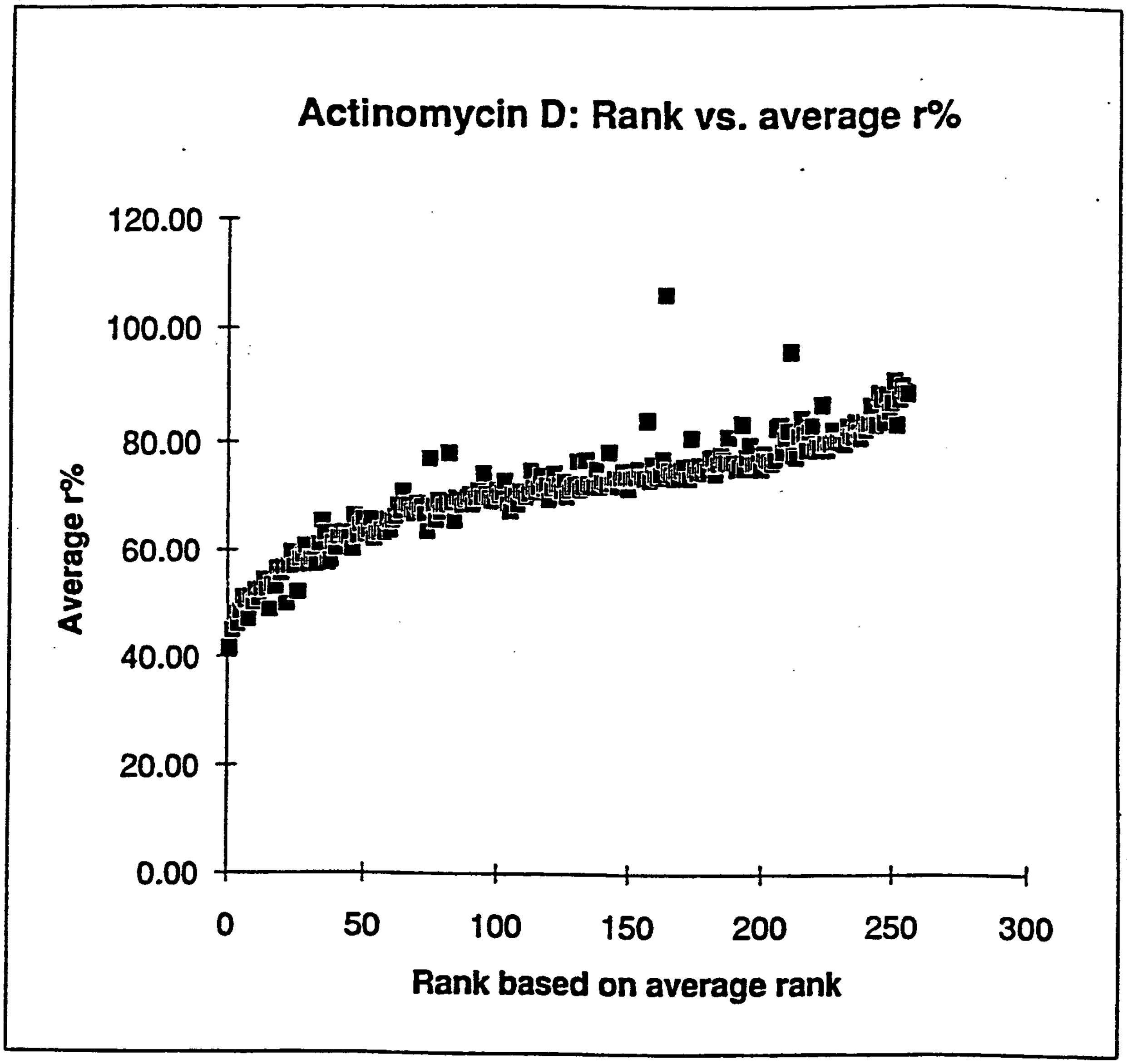


Fig. 19

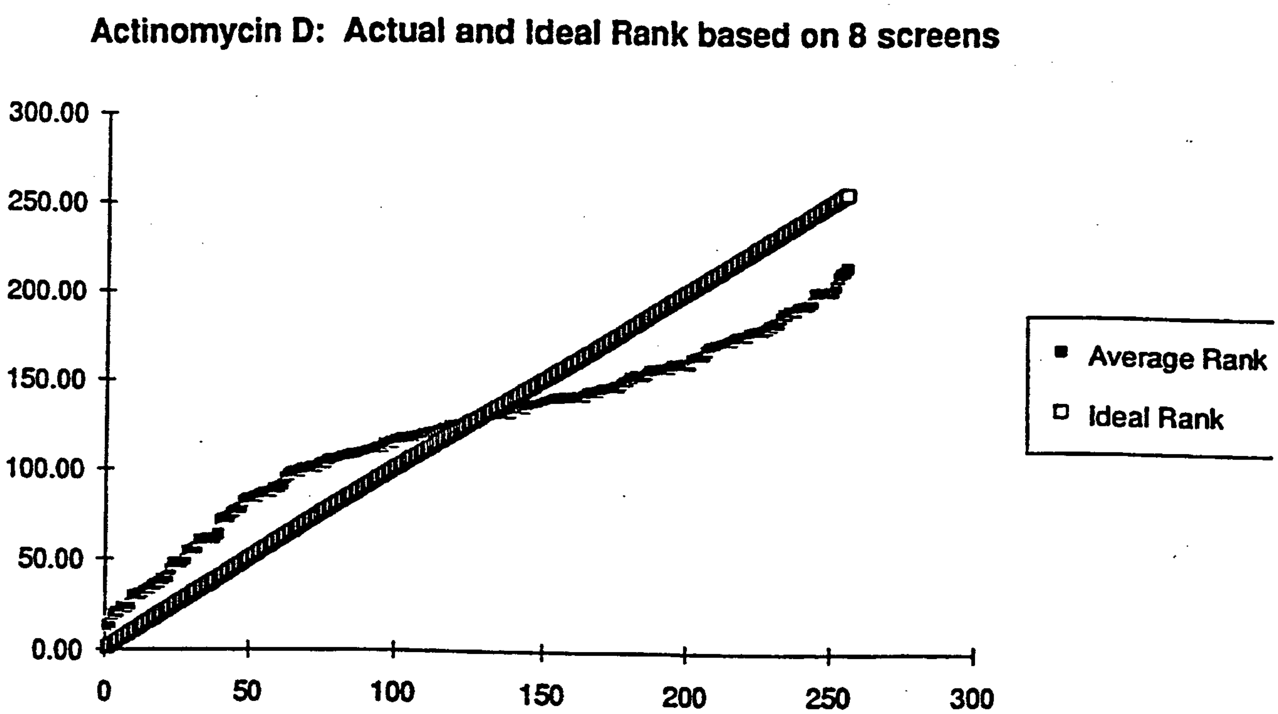

Actinomycin D: Actual and Ideal Rank based on 8 screens
300.00
250.00
200.00
150.00
100.00
50.00
0.00
0
50
100
150
200
250
300
Average Rank
Ideal Rank

Fig. 20

Actinomycin D: Variance from mean	
A1	-4.38
C1	1.09
G1	7.71
T1	-4.42
A2	-0.29
C2	4.39
G2	-4.02
T2	-0.08
A3	2.29
C3	-4.88
G3	2.86
T3	-0.27
A4	-0.92
C4	2.01
G4	0.56
T4	-1.65

Fig. 21

	N1N2	N1N3	N1N4	N2N3	N2N4	N3N4	XNX	XX
AA	-3.39	-0.94	-4.21	0.80	-2.00	2.56	-1.47	-0.01
AC	-3.00	-10.57	-2.04	-3.61	2.28	1.72	-4.14	-1.63
AG	-10.85	-2.35	-3.13	2.14	0.89	1.29	-0.73	-2.47
AT	-0.25	-3.64	-8.12	-0.49	-2.33	3.58	-2.98	0.95
CA	1.52	1.61	-1.63	7.80	3.78	-3.33	2.69	2.00
CC	2.14	-2.89	4.97	-4.43	4.63	-5.45	0.87	-2.58
CG	-1.38	5.44	2.58	8.94	5.72	-3.56	5.58	1.33
CT	2.08	0.20	-1.55	5.26	3.44	-7.19	1.82	0.05
GA	-1.48	9.81	6.63	1.08	-3.47	-1.31	3.17	-0.57
GC	23.80	2.40	7.64	-7.41	-1.51	9.80	0.44	8.73
GG	10.42	11.66	7.28	-4.76	-4.87	5.21	3.39	3.62
GT	-1.89	6.96	9.30	-5.00	-6.22	-2.27	0.37	-3.05
TA	2.19	-1.33	-4.47	-0.54	-1.99	-1.60	-1.66	0.02
TC	-5.36	-8.47	-2.54	-4.07	2.63	1.95	-2.92	-2.49
TG	-14.27	-3.31	-4.46	5.12	0.52	-0.69	-1.39	-3.28
TT	-0.26	-4.59	-6.22	-0.84	-1.49	-0.72	-3.04	-0.61
stdev:	8.44	6.13	5.54	4.86	3.52	4.22	2.78	3.04

Fig. 22

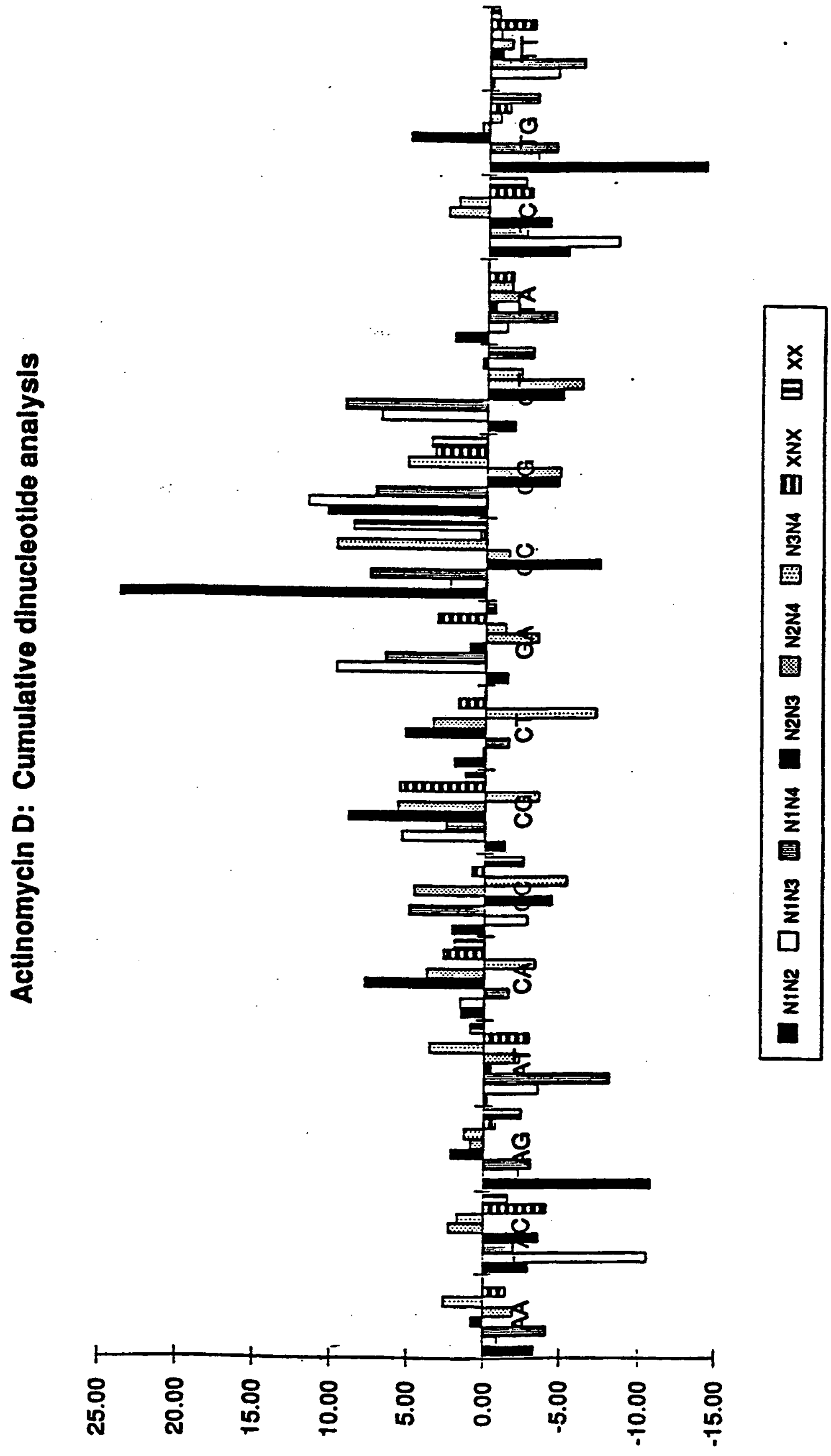

Actinomycin D: Cumulative dinucleotide analysis
25.00
20.00
15.00
10.00
5.00
0.00
-5.00
-10.00
-15.00
AA
AC
AG
AT
CA
CG
CT
GA
TA
TC
TG
TT
N1N2
N1N3
N1N4
N2N3
N2N4
N3N4
XNX
XX

Fig 23

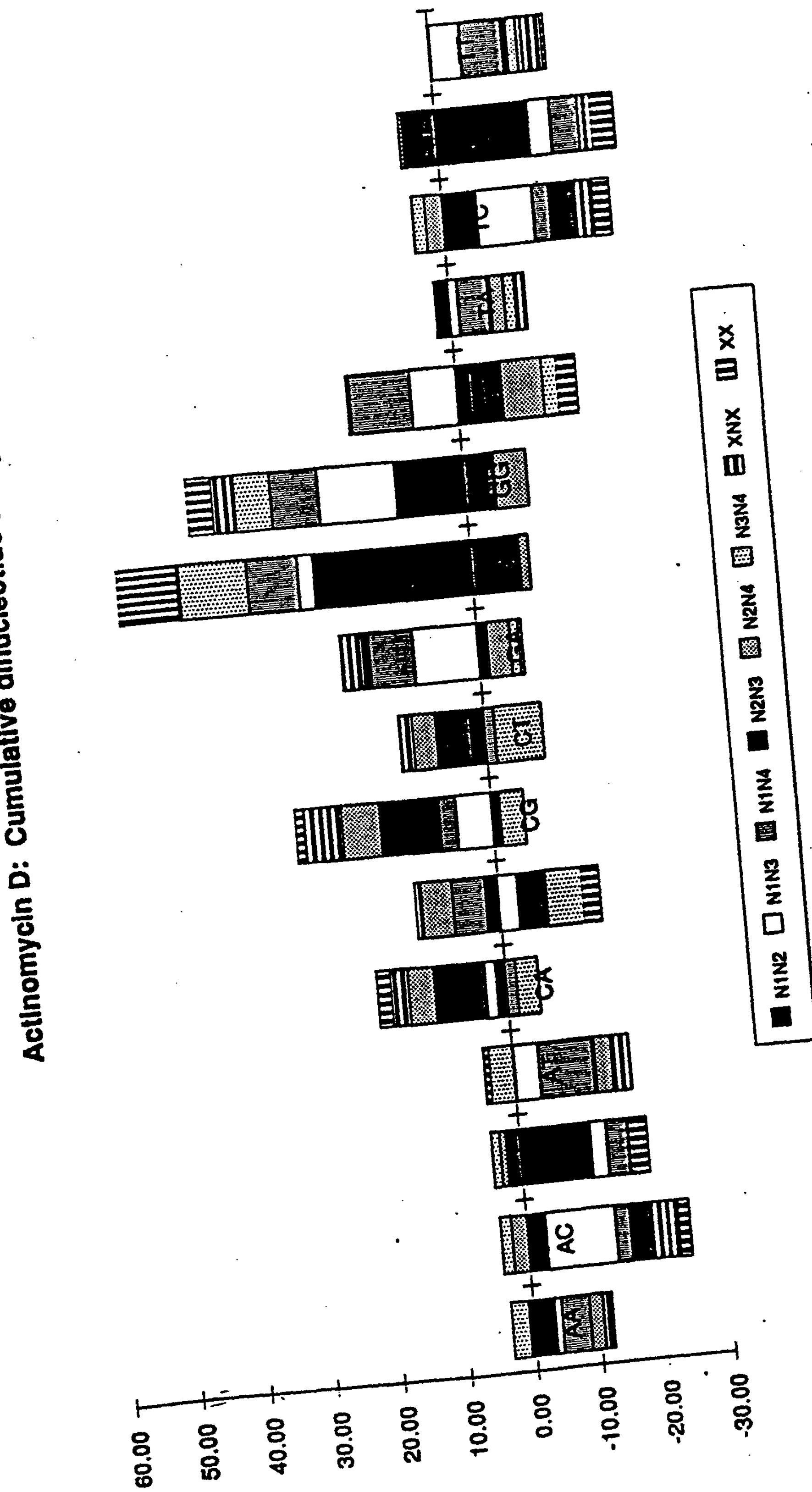

Actinomycin D: Cumulative dinucleotide analysis
60.00
50.00
40.00
30.00
20.00
10.00
0.00
-10.00
-20.00
-30.00
AA
AC
CA
CG
CT
GG
N1N2
N1N3
N1N4
N2N3
N2N4
N3N4
XNX
XX

Fig. 24

Fig. 25

TTCCTTCC	TTACTTCC	TACCTTCC	TAACTTCC
TTCCTTAC	TTACTTAC	TACCTTAC	TAACTTAC
TTCCTACC	TTACTACC	TACCTACC	TAACTACC
TTCCTAAC	TTACTAAC	TACCTAAC	TAACTAAC

Fig. 26

TTCCNTTCC
TTCCNNTTCC
TTCCNNNTTCC
TTCCNNNNTTCC

Fig. 27A

```
      --->  --UL9-->  --->
5'-GCGTANXYZZCGTTCGCACTTXYZZCTTCGTCCCAAT-3'
3'-CGCATNYXQQGCAAGCGTGAAYXQQGAAGCAGGGTTA-5'
```

Score high

Fig. 27B

```
            --UL9-->
5'-GCGTANQQXYCGTTCGCACTTQQXYCTTCGTCCCAAT-3'
3'-CGCATNZZYXGCAAGCGTGAAZZYXGAAGCAGGGTTA-5'
      <---                <---
```

Score low

Fig. 27C

```
      --->                --->
5'-GCGTANXYZZTTCACGCTTGCXYZZCTTCGTCCCAAT-3'
3'-CGCATNYXQQAAGTGCGAACGYXQQGAAGCAGGGTTA-5'
           <--UL9---
```

Fig. 27D

```
5'-GCGTANQQXYTTCACGCTTGCQQXYCTTCGTCCCAAT-3'
3'-CGCATNZZYXAAGTGCGAACGZZYXGAAGCAGGGTTA-5'
      <---  <--UL9---  <---
```

Fig. 27E

```
      --->  --UL9-->
5'-GCGTANXYZZCGTTCGCACTTQQXYCTTCGTCCCAAT-3'
3'-CGCATNYXQQGCAAGCGTGAAZZYXGAAGCAGGGTTA-5'
                          <---
```

Fig. 27F

```
            --UL9-->  --->
5'-GCGTANQQXYCGTTCGCACTTXYZZCTTCGTCCCAAT-3'
3'-CGCATNZZYXGCAAGCGTGAAYXQQGAAGCAGGGTTA-5'
      <---
```

Fig. 27G

```
      --->
5'-GCGTANXYZZTTCACGCTTGCQQXYCTTCGTCCCAAT-3'
3'-CGCATNYXQQAAGTGCGAACGZZYXGAAGCAGGGTTA-5'
           <--UL9---  <---
```

Fig. 27H

```
                          --->
5'-GCGTANQQXYTTCACGCTTGCXYZZCTTCGTCCCAAT-3'
3'-CGCATNZZYXAAGTGCGAACGYXQQGAAGCAGGGTTA-5'
      <---  <--UL9---
```

```
     HIVBH101 (HIV LTR sequence)
GTTAGAGTGG AGGTTTGACA GCCGCCTAGC ATTTCATCAC ATGGCCCGAG
                                                     ¦
AGCTGCATCC GGAGTACTTC AAGAACTGCT GACATCGAGC TTGCTACAAG
<<NF-κB>>¦   ¦<<<NF-κB>>¦    ¦<Sp-1 III¦   ¦<Sp-1 II¦  ¦<
GGACTTTCCG CTGGGGACTT TCCAGGGAGG CGTGGCCTGG GCGGGACTGG
Sp-1 I>¦                    ¦TATA¦
GGAGTGGCGA GCCCTCAGAT CCTGCATATA AGCAGCTGCT TTTTGCCTGT
            +1 prim transcript start --->
ACTG GGTCTCTCTGGTTAGACCAGATCTGAGCCTGGGAGCTC
```

Fig. 28

Fig. 29A

```
           EcoRI/PstI
             primer
5'-GCAGAATTCTGCAG-3'   UL9 site
5'-GCAGAATTCTGCAG(N)xCGTTCGCACTTTCTAGAGCTCAGG-3'
3'-CGTCTTAAGACGTC(N)xGCAAGCGTGAAAGATCTCGAGTCC-5'
                 test       3'-AGATCTCGAGTCC-5'
                 site            XbaI/SacI
                                 primer
```

where X is the number of bases in the test site.

Fig. 29B

5'-GCAGAATTCTGCAGNNNNCGTTCGCACTTTCTAGAGCTCAGG-3'

Fig. 29C

5'-GCAGAATTCTGCAGNNNNNNNNNCGTTCGCACTTTCTAGAGCTCAGG-3'

Fig. 29D

5'-GCAGAATTCTGCAGCGTTCGCACTTNNNNNNNNNTCTAGAGCTCAGG-3'

UL9 Site 3' relative to th t st s quence:

```
      primers
    EcoRI/PstI
5'-CGTGAATTCTGCAG-3'
5'-CGTGAATTCTGCAGATG-3'

                    Asp718/RsaI/KpnI
                      restriction
                         site        UL9 site
5'-CGTGAATTCTGCAGATGAGGTACCNNNNNNCGTTCGCACTTTCTAGAGCTCTCC
                              test
                              site
                                       GTGAAAGATCTCGAGAGG- 5'
                                          AAGATCTCGAGAGG- 5'
                                            XbaI/SacI
                                             primers
```

Fig. 30

Small Molecule Binding Sequence	Expected Score in Assay	Potential Test Site Sequenc
UL9 site 5'-...CGTTCGCACTTTTAC...-3'	high	TTAC
5'-...CGTTCGCACTTTACN...-3'	high	TACN
5'-...CGTTCGCACTTACNN...-3'	high	ACNN

Fig. 31

Small Molecule Binding Sequence	Expected Score in Assay	Potential Test Site Sequenc
SmaI 5'-...CCCGGGTTAC...-3'	high	TTAC
5'-...CCCGGGTACN...-3'	low	TACN
5'-...CCCGGGACNN...-3'	low	ACNN

Fig. 32

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/12388

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :Please See Extra Sheet.
US CL :435/6, 235; 514/44; 530/350, 351; 536/23.1, 23.2
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6, 235; 514/44; 530/350, 351; 536/23.1, 23.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE, DIALOG

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 5,071,773 (EVANS ET AL) 10 December 1991.	1-44
A	US, A, 5,096,815 (LADNER ET AL) 17 March 1992.	1-44

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 MARCH 1994	APR 19 1994

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	GIAN WANG Jill Warden for
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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/12388

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (5):

C12Q 1/68; C12N 7/00; A01N 43/04; A61K 31/70; C07K 3/00, 13/00, 15/00, 17/00; C07H 17/00